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	 [-JUS]: 1981 Duxbury Way, Cheuterfield, MO 63017 (US), I., Jinglin, J. (USVUS): 76 Standard Road East, Pennington, MO 8334 (US), MILLER, Raymond, E. (USVUS): 9904 Old Lincoln Trail, Fairriew Height, IL 62226 (US), RETTZ, David, B. (USVUS): 14814 Pleasant Ridge, Chesterfield, MO 63017 (US), TREMONT, Samuel, J. (USVUS): 729 Berquist Drive, St. Louis, MO 63011 (US). 	entorry, and entorry Applicants (for US only); LEB, Lea, F. [USUS]; entorry Applicants (for US only); LEB, Lea, F. [USUS]; 296 Annually Way, St. Culy; 1556 Country Ridge Drive, Chenterfield, MO 53017 (US); HUANG, Homg-Chib Drive, Chenterfield, MO 53017 (US); HUANG, Homg-Chib	pikenti (for all designated States except US); G.D. SBARLB & CO. (US/US); Corporate Patent Department, P.O. Box 5110, Chicago, II. 60680-5110 (US).	ority Data 09/109,551	national national	C07D 337/08, 487/08, 409/12, 409/10, C07K \$/06, C07F 9/6533, C07C 323/18, A61K 31/38	rational	INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
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TAUROCHOLATE UPTAKE

(57) Abstract

FOR THE PURPOSES OF INFORMATION ONLY

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NOVEL BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

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BACKGROUND OF THE INVENTION

Field of the Invention

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The present invention relates to novel benzothiepines, derivatives and analogs thereof, pharmaceutical compositions containing them, and their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as is associated with atherosclerosis or hypercholesterolemia, in mammals.

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Description of Related Art

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It is well-settled that hyperlipidemic conditions state of atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents are major risk factors for coronary heart disease and such reduction leads to an improvement in the disease naving hypocholesterolemic properties," Biochimica et particularly atherosclerosis. Interfering with the Epidemiological data has accumulated which indicates cholesterol and low-density lipoprotein cholesterol 31ophysica Acta, 1210 (1994) 255-287 discusses the intestinal tract is found to reduce the levels of circulation of bile acids within the lumen of the associated with elevated concentrations of total biochemistry, physiology and known active agents serum cholesterol in a causal relationship. surrounding bile acids and cholesterol

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Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic

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circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport",

Gastroenterology, 1982:83:804-11.
In fact, cholestyramine binds the bile acids in

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the intestinal tract, thereby interfering with their normal enterohepatic circulation (Reihnér, E. et al, in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein receptor expression in gallstone patients", <u>Journal of Lipid Research</u>, Volume 31, 1990, 2219-2226 and Suckling el al, "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", <u>Atherosclerosis</u>, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol

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In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 25, pp. 18035-18046, 1993).

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levels.

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In a series of patent applications, e.g. Canadian Patent Application Nos. 2,025,234; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731; Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including

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cholesterol level sufficiently to be effective as transport with the goal of reducing the LDL bile acid, which inhibit the physiological bile acid hypocholesterolemic agents. pharmaceuticals and, in particular for use as

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"Hypolipidemic Benzothiazepine Compounds" patent application number WO 93/16055 for Wellcome Foundation Limited disclosure of the world disclosed to show hypolipidemic activity in The In vitro bile acid transport inhibition is

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uses including fatty acid metabolism and coronary patent application number WO93/321146 for numerous vascular diseases. Selected benzothiepines are disclosed in world

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phenyl ring of the fused bicyclo benzothiepine ring. 508425, FR 2661676, and WO 92/18462, each of which is atherosclerosis as disclosed by application Nos. EP especially for the treatment or prevention of limited by an amide bonded to the carbon adjacent the as hypolipaemic and hypocholesterolaemic agents, Other selected benzothiepines are known for use

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usefulness as hypocholesterolemic agents. treatment of hyperlipidemic diseases and their find safe, effective agents for the prophylaxis and The above references show continuing efforts to

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89/1477/A as abstracted in Derwent Abstract No. 89-Derwent Abstr. No. 65860T-B and WO 92/18462. US 3,287,370, US 3,389,144; US 3,694,446 abstracted in 370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; as abstracted by Derwent Abstract No. 93-351589; WO the present invention utility. These are EP 568 898A disclosed for use in various disease states not within Additionally selected benzothiepines are

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providing novel benzothiepines, pharmaceutical compositions, and methods of use therefor. The present invention furthers such efforts by

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SUMMARY OF THE INVENTION

present invention provides compounds of formula (1): Accordingly, among its various apects, the

wherein:

q is an integer from 1 to 4; n is an integer from 0 to 2;

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group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, \mathbb{R}^{2} and \mathbb{R}^{2} are independently selected from the

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 $S(0)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, $O(2R^9)$, $O(2R^9)$ OR9, NR9R10, N+R9R10RWA-, SR9, S'R'R"A: P+R9R10R11Asubstituents selected from the group consisting of cycloalkyl optionally are substituted with one or more dialkylamino, alkylthio, (polyalkyl)aryl, and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, wherein alkyl, alkenyl, alkynyl, haloalkyl,

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NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, Or optionally have one or more carbons replaced by 0, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl wherein alkyl, alkenyl, alkynyl, alkylaryl,

phenylene,

alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, selected from the group consisting of H, alkyl, wherein R9, R10, and RW are independently heterocyclylalkyl, and alkylammoniumalkyl; or carboxyalkylaminoalkyl, heteroarylalkyl, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino,

 ${\bf R}^1$ and ${\bf R}^2$ taken together with the carbon to which ${\rm R}^3$ and ${\rm R}^4$ are independently selected from the they are attached form C3-C10 cycloalkyl;

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acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO2R9, and SO3R9, wherein R and R are as defined group consisting of H, alkyl, alkenyl, alkynyl, above; or

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R³ and R⁴ together form =0, =NOR¹¹, =S, "NNR¹¹R¹², "NR⁹, or "CR¹¹R¹²,

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wherein R⁹ and R¹⁰ are as defined above, provided that ılkymyl, aryl, arylalkyl, alkenylalkyl, alkymylalkyl, wherein R¹¹ and R¹² are independently selected ${
m SO_2R^9},~{
m SO_3R^9},~{
m CO_2R^9},~{
m CN},~{
m halogen},~{
m oxo},~{
m and}~{
m CONR^9R^{10}},$ cycloalkyl, cyanoalkyl, \mathtt{OR}^9 , $\mathtt{NR}^9\mathtt{R}^{10}$, \mathtt{SR}^9 , $\mathtt{S(0)R}^9$, from the group consisting of H, alkyl, alkenyl, neterocycle, carboxyalkyl, carboalkoxyalkyl, both R3 and R4 cannot be OH, NH2, and SH, or

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 R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR⁹ ${\rm R}^5$ and ${\rm R}^6$ are independently selected from the

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SR⁹, 8(0)R⁹, SO₂R⁹, and SO₃R⁹

wherein alkyl, alkenyl, alkynyl, aryl,

NR¹³SO₂R¹⁴, NR¹³SONR¹⁴R¹⁵, NR¹³SO₂NR¹⁴R¹⁵, P(0)R¹³R¹⁴ cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, ${
m No_2}$, ${
m Co_2}{
m R}^{13}$, CN, OM, ${
m So_2}{
m OM}$, ${
m So_2}{
m NR}^{13}{
m R}^{14}$, C(O) ${
m NR}^{13}{
m R}^{14}$, more substituent groups independently selected from quaternary heteroaryl, halogen, oxo, OR¹³, NR¹³R¹⁴, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkymyl, neterocycle, arylalkyl, quaternary heterocycle, ${
m NR}^{13}{
m Co}_2{
m R}^{14}$, oc(0) ${
m R}^{13}$, oc(0) ${
m NR}^{13}{
m R}^{14}$, ${
m NR}^{13}{
m SoR}^{14}$, c(0)OM, cor^{13}_{13} , $NR^{13}c(0)R^{14}$, $NR^{13}c(0)NR^{14}R^{15}$, P+R13R14R15A-, P(OR13)OR14, S+R13R14A-, and

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N+R9R11R12A-,

wherein:

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

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consisting of OR^7 , $\operatorname{NR}^7 \operatorname{R}^8$, SR^7 , $\operatorname{S}(\operatorname{O}) \operatorname{R}^7$, $\operatorname{SO}_2 \operatorname{R}^7$, $\operatorname{SO}_3 \operatorname{R}^7$, CO2R7, CN, OXO, CONR7R8, N*R7R8R9A-, alkyl, alkenyl, heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, nore substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, (0) R7R8, p+R7R8R9A-, and P(0) (OR7) OR8, and polyether, aryl, haloalkyl, cycloalkyl, and

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, heterocycle can optionally have one or more carbons polyether, aryl, haloalkyl, cycloalkyl, and

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quaternary heteroarylalkyl, alkoxyalkyl, $P(0)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} carboxyalkylaminocarbonylalkyl, alkylammoniumalkyl, and cycloalkyl, heterocycle, heteroaryl, quaternary heteroarylalkyl, quaternary heterocyclylalkyl, heterocycle, quaternary heteroaryl, heterocyclylalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, are independently selected from the group consisting replaced by 0, NR^7 , $N^+R^7R^8A^-$, S, SO, SO₂, $S^+R^7A^-$, PR^7

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carbohydrate, amino acid, peptide, or polypeptide, and S⁺R⁹A', PR⁹, P⁺R⁹R¹⁰A-, P(O)R⁹, phenylene, carbons replaced by O, NR9, N+R9R10A-, S, SO, SO2, heterocycle, and polyalkyl optionally have one or more $^{
m R^{13},\ R^{14}}$, and $^{
m R^{15}}$ are optionally substituted with wherein alkyl, alkenyl, alkynyl, arylalkyl,

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heteroarylalkyl, guanidinyl, quaternary heterocyclylalkyl, quaternary quaternary heterocycle, quaternary heteroaryl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl of hydroxy, amino, sulfo, carboxy, alkyl, one or more groups selected from the group consisting

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 $p^{+}R^{9}R^{10}R^{11}A^{-}$, $s^{+}R^{9}R^{10}A^{-}$, and C(0)OM, $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, OXO_{4} , OXO_{4} CN, halogen, $\operatorname{CONR}^9 \operatorname{R}^{10}$, $\operatorname{SO}_2 \operatorname{OM}$, $\operatorname{SO}_2 \operatorname{NR}^9 \operatorname{R}^{10}$, $\operatorname{PO}(\operatorname{OR}^{16}) \operatorname{OR}^{17}$ carboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰

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from the substituents constituting R9 and M; or $m R^{13}~and~R^{14}$, together with the nitrogen atom to wherein R^{16} and R^{17} are independently selected

which they are attached form a mono- or polycyclic

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oxo, carboxy and quaternary salts; or more radicals selected from the group consisting of heterocycle that is optionally substituted with one

which they are attached, form a cyclic ring; and ${ t R}^7$ and ${ t R}^8$ are independently selected from the ${
m R}^{14}$ and ${
m R}^{15}$, together with the nitrogen atom to

group consisting of hydrogen and alkyl; and one or more RX are independently selected from

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 $m p^{+}R^{9}R^{11}R^{12}A^{-}$, amino acid, peptide, polypeptide, $S(0)_{\rm D}NR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^{+}R^{9}R^{11}R^{12}A^{-}$, $C(0)NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, C(0)OM, COR^{13} , OR^{18} CO2R¹³, CN, OM, SO2OM, SO2NR¹³R¹⁴, NR¹⁴C(O)R¹³ the group consisting of H, alkyl, alkenyl, alkynyl, carbohydrate, SO3R13, S+R13R14A-, NR13OR14, NR13NR14R15, NO2, heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³; S(O)₂R¹³ polyether, quaternary heterocycle, quaternary polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl,

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25 20 $PO(OR^{16})OR^{17}$, $P^{+}R^{9}R^{11}R^{12}A^{-}$, $S^{+}R^{9}R^{10}A^{-}$, or C(O)OM, and oxo, CO2R9, CN, halogen, CONR9R10, SO2OM, SO2NR9R10 oR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹ haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, quaternary heteroaryl can be further substituted with wherein alkyl, alkenyl, alkynyl, cycloalkyl,

of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, wherein \mathbb{R}^{18} is selected from the group consisting

heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are wherein acyl, arylalkoxycarbonyl, arylalkyl,

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substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^4R^9R^{11}R^{12}A^-$, SR^9 , $S(0)R^9$, SO_2R^9 , SO_3R^9 , OXO, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO\left(OR^{16}\right)OR^{17}$, and C(0)OM,

wherein in R^{x} , one or more carbons are optionally replaced by 0, NR^{13} , $N^{+}R^{13}R^{14}A^{-}$, S, SO, SO₂, $S^{+}R^{13}A^{-}$, PR^{13} , $P(0)R^{13}$, $P^{+}R^{13}R^{14}A^{-}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

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wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, S, SO, SO₂, S⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(O)R⁹;

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wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, oR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₂R¹³, SO₂OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, P(O)R¹³R¹⁴, P¹R¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴, S¹R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻,

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provided that both $\rm R^5$ and $\rm R^6$ cannot be hydrogen, OH, or SH and when $\rm R^5$ is OH, $\rm R^1$, $\rm R^2$, $\rm R^3$, $\rm R^4$, $\rm R^7$ and $\rm R^8$ cannot be all hydrogen;

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provided that when R* or R* is phenyl, only one of R¹ or R² is H,

provided that when q = 1 and R^{x} is styryl,

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anilido, or anilinocarbonyl, only one of \mathbb{R}^5 or \mathbb{R}^6 is alkyl;

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alkyl; provided that when n is 1, R^1 , R^3 , R^7 , and R^8 are

hydrogen, R² is hydrogen, alkyl or aryl, R⁴ is unsubstituted amino or amino substituted with one or more alkyl or aryl radicals, and R⁵ is hydrogen, alkyl or aryl, then R⁶ is other than hydroxy; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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Preferably, $\rm R^5$ and $\rm R^6$ can independently be selected from the group consisting of H, aryl, neterocycle, quaternary heterocycle, and quaternary neteroaryl,

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wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, haloach, oxo, OR13, NR13R14, SR13, S(O)R13, SO2R13, SO2R13, NR13C(O)R13R14, C(O)NR13R14, C(O)OM, COR13, NR13C(O)R13R14, NR13SO2R14, NR13R14, P*R13R14R15A-, P(OR1)OR14, S+R1814-, and N*R8R1R12A-,

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N^{*}R⁷R⁸A-, S, SO, SO₂, S^{*}R⁷A-, PR⁷,

 $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$. quaternary heterocycle, quaternary heteroaryl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^4R^7R^8R^9A^7$, alkyl, alkenyl, $P(0)R^7$, $P^{\dagger}R^7R^8A^-$, or phenylene, consisting of OR^7 , NR^7R^8 , SR^7 , $S(0)R^7$, SO_2R^7 , SO_3R^7 more substituent groups selected from the group polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or wherein said alkyl, alkenyl, alkynyl, polyalkyl,

More preferably, R⁵ or R⁶ has the formula:

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-Ax-(RY) t

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t is an integer from 0 to 5;

benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; triazolyl, isothiazolyl, indolyl, benzoimidazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, Ar is selected from the group consisting of

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C(0) 0M, COR 13, NR 13 C(0) R 14, NR 13 C(0) NR 14 R 15, NO2, CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$ polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴ the group consisting of alkyl, alkenyl, alkynyl, 3 , $_{8}$ (0) $_{R}$ 13 , $_{90}$ $_{R}$ 13 , $_{13}$ $_{0R}$ 14 , $_{13}$ $_{NR}$ 14 $_{R}$ 15 one or more RY are independently selected from

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NR¹³SO₂R¹⁴, NR¹³SONR¹⁴R¹⁵, NR¹³SO₂NR¹⁴R¹⁵, P(0)R¹³R¹⁴ N+R9R11R12A-, $p^{+}R^{13}R^{14}R^{15}A^{-}$, $P(OR^{13})OR^{14}$, $S^{+}R^{13}R^{14}A^{-}$, and $NR^{13}CO_2R^{14}$, OC(0)R¹³, OC(0)NR¹³R¹⁴, NR¹³SOR¹⁴

 CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, replaced by 0, NR7, N+R7R8A-, s, so, so2, s+R7A-, PR7, polyether, aryl, haloalkyl, cycloalkyl, and $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$, and $P(0)R^{7}$, $P^{4}R^{7}R^{8}A^{-}$, or phenylene quaternary heterocycle, quaternary heteroaryl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, heterocycle can optionally have one or more carbons consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 more substituent groups selected from the group polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or wherein said alkyl, alkenyl, alkynyl, polyalkyl wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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20 (II) : Still more preferably, R5 or R6 has the formula

(II)

consists of those compounds of formula I wherein A first class of compounds of particular interest 25

q is 1 or 2;

n 18 2;

R' and R' are each alkyl;

R' is hydroxy;

R' and R' are hydrogen;

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has the formula (II)

(II)

2

wherein t is an integer from 0 to 5;

one or more R' are OR¹³;

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R¹³ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, alkylarylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroarylalkyl;

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said R¹³ alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR², N'R²R²A', S, SO, SO₂, S'R³A', PR³, P'R²R³A', P(O)R³, phenylene, carbohydrate, amino acid, peptide, or polypeptide;

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R¹³ is optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR*, NR*R**, NYR*R**R**, SO,R*, SO,R*, CN, halogen, CONR*R*, SO,OM, SO,NR*R**, PO(OR**)OR**, P'R*R**R**, ST*R**R**, and C(O)OM,

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wherein A is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation,

 R^{\bullet} and R^{10} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

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,

cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, cycloalkyl, cycloalkyl, cyanoalkyl, OR, NR,¹⁰, SR, S(O)R', SO,R', SO,R', CO,R', CN, halogen, oxo, and CONR'R', wherein R' and R' are as defined above, provided that both R' and R' cannot be OH, NH, and SH; or

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 R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring; and

and R¹⁴ and R¹⁷ are independently selected from the

R' and R' are hydrogen; and

substituents constituting R' and M;

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one or more R² are independently selected from the group consisting of alkoxy, alkylamino and dialkylamino; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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A second class of compounds of particular interest consists of those compounds of formula I

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q is an integer from 1 to 4; n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

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wherein alkyl, alkenyl, alkynyl, haloalkyl,
alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,
dialkylamino, alkylthio, (polyalkyl)aryl, and

phenylene, NR⁹, N⁺R⁹R¹⁰A-, s, so, so₂, s⁺R⁹A⁻, p⁺R⁹R¹⁰A⁻, or optionally have one or more carbons replaced by O, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl wherein alkyl, alkenyl, alkynyl, alkylaryl,

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CONR9R10

carboxyheteroaryl, carboxyheterocycle, heterocyclylalkyl, and alkylammoniumalkyl; or carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, selected from the group consisting of H, alkyl, ammoniumalkyl, arylalkyl, carboxyalkyl, ${ t R}^1$ and ${ t R}^2$ taken together with the carbon to which wherein R^9 , R^{10} , and R^W are independently

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SO2R9, and SO3R9, wherein R' and R' are as defined above; or acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹ group consisting of H, alkyl, alkenyl, alkynyl, ${ t R}^3$ and ${ t R}^4$ are independently selected from the

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they are attached form C,-C10 cycloalkyl;

-NNR 11 R 12, -NR 9, or -CR 11 R 12, R^3 and R^4 together form =0, =NOR 11 , =S

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SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰ cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, heterocycle, carboxyalkyl, carboalkoxyalkyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, from the group consisting of H, alkyl, alkenyl, wherein R^{11} and R^{12} are independently selected

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both R3 and R4 cannot be OH, NH2, and SH, or wherein ${ t R}^9$ and ${ t R}^{10}$ are as defined above, provided that

atom to which they are attached form a cyclic ring; \mathbb{R}^{11} and \mathbb{R}^{12} together with the nitrogen or carbon R^5 is aryl substituted with one or more OR^{13a}

carboxyalkylaminocarbonylalkyl, alkylammoniumalkyl, and heteroarylalkyl, quaternary heterocyclylalkyl, alkylheterocyclylalkyl, heterocyclylalkyl, consisting of alkylarylalkyl, alkylheteroarylalkyl, wherein R^{13a} is selected from the group

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 $s^+R^9R^{10}A^-$, and C(0)OM, SO20M, SO2NR9R10, PO(OR16)OR17, P+R9R10R11A-, SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰ guanidinyl, oR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹ heterocyclylalkyl, quaternary heteroarylalkyl, heterocycle, quaternary heteroaryl, quaternary groups selected from the group consisting of hydroxy, heterocycle, heteroaryl, sulfoalkyl, quaternary amino, sulfo, carboxy, alkyl, carboxyalkyl, ${f R}^{f 13a}$ is optionally substituted with one or more

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anion and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable 20

from the substituents constituting R^9 and M_1 and \cdots wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected

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s(0)R9, so2R9, and so3R9, heterocycle, quaternary heterocycle, OR30, SR9 alkyl, alkenyl, alkynyl, aryl, cycloalkyl, ${ t R}^6$ is selected from the group consisting of H,

30 cycloalkyl, heterocycle, quaternary heterocycle, and wherein alkyl, alkenyl, alkynyl, aryl,

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SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, more substituent groups independently selected from NO2, CO2R¹³, CN, OM, SO2OM, SO2NR¹³R¹⁴, C(O)NR¹³R¹⁴, OC(0)R11, OC(0)NR11R14, NR11SOR14, NR11SO,R14, NR11SONR14R18 NR1150,NR14R15, P(0)R13R14, P+R13R14R15A-, P(OR13)OR14 quaternary heteroaryl, halogen, oxo, OR^{13} , $\mathrm{NR}^{13}\mathrm{R}^{14}$ C(0) OM, COR¹³, NR¹³C(0) R¹⁴, NR¹³C(0) NR¹⁴R¹⁵, NR¹³CO₂R¹⁴, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, quaternary heteroaryl can be substituted with one the group consisting of alkyl, alkenyl, alkynyl, heterocycle, arylalkyl, quaternary heterocycle, S+R13R14A-, and N+R9R11R12A-,

ß

wherein:

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A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

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consisting of OR7, NR7R8, SR7, S(O)R7, SO2R7, SO3R7, CO2R7, CN, oxo, CONR7R8, N+R7R8R9A-, alkyl, alkenyl, heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, more substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and P(0) R⁷R⁸, P⁺R⁷R⁹R⁹A⁻, and P(0) (OR⁷) OR⁸, and

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replaced by 0, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R7, P*R7R8A-, or phenylene, and R13, R14, and R15 wherein said alkyl, alkenyl, alkymyl, polyalkyl, are independently selected from the group consisting heterocycle can optionally have one or more carbons of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and polyether, aryl, arylalkyl, alkylarylalkyl,

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heterocycle, quaternary heteroaryl, heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and cycloalkyl, heterocycle, heteroaryl, quaternary neteroarylalkyl, quaternary heterocyclylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, carboxyalkylaminocarbonylalkyl,

neterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', N⁺R⁹R¹⁰A-, S, SO, SO₂, wherein alkyl, alkenyl, alkynyl, arylalkyl,

sarbohydrate, amino acid, peptide, or polypeptide, and S+R9A', PR9, P+R9R10A-, P(O)R', phenylene, ដ

R¹³, R¹⁴, and R¹⁵ are optionally substituted with neteroarylalkyl, guanidinyl, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^$ one or more groups selected from the group consisting carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, of hydroxy, amino, sulfo, carboxy, alkyl, juaternary heterocyclylalkyl, quaternary

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 $\mathsf{conr}^9 \mathsf{R}^{10}$, $\mathsf{so}_2 \mathsf{om}$, $\mathsf{so}_2 \mathsf{NR}^9 \mathsf{R}^{10}$, $\mathsf{po}(\mathsf{oR}^{16}) \mathsf{oR}^{17}$, $\mathsf{p}^+ \mathsf{R}^9 \mathsf{R}^{10} \mathsf{R}^{11} \mathsf{A}^-$ SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, Oxo, CO₂R⁹, CN, halogen, S+R9R10A-, and C(O)OM,

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meterocycle that is optionally substituted with one or nore radicals selected from the group consisting of wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic from the substituents constituting R9 and M; or oxo, carboxy and quaternary salts; or

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 R^{14} and R^{15} , together with the nitrogen atom to R is selected from the group consisting of which they are attached, form a cyclic ring; and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl,

group consisting of hydrogen and alkyl; and \mathbb{R}^7 and \mathbb{R}^8 are independently selected from the

 $C(0)NR^{13}R^{14}$, NR14C(0)R13, C(0)OM, COR^{13} , OR^{18} carbohydrate, $\mathfrak{p}^+\mathfrak{R}^0\mathfrak{R}^{11}\mathfrak{R}^{12}\mathfrak{A}^-$, amino acid, peptide, polypeptide, and $S(0)_{\rm D}NR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^{+}R^{9}R^{11}R^{12}A^{-}$, CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, SO3R13, S+R13R14A-, NR13OR14, NR13NR14R15, NO2, heteroaryl, OR13, NR13R14, SR13, S(0)R13, S(0)2R13, polyether, quaternary heterocycle, quaternary haloalkyl, cycloalkyl, heterocycle, heteroaryl, the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, one or more $R^{\mathbf{X}}$ are independently selected from

5

5

or9, NR9R10, N+R9R11R12A-, SR9, S(0)R9, SO2R9, SO3R9 quaternary heteroaryl can be further substituted with haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl

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of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, wherein R^{18} is selected from the group consisting

PO(OR1)OR17, P+R9R11R12A-, S+R9R10A-, or C(0)OM, and

oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰

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heterocycle, heteroaryl, alkyl, quaternary substituted with one or more substituents selected heterocycle, and quaternary heteroaryl optionally are wherein acyl, arylalkoxycarbonyl, arylalkyl,

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, SR^9 , $S(0)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, C(0)0M, CONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and from the group consisting of OR 9 , NR 9 R 10 , N $^+$ R 9 R 11 R 12 A $^-$

 pR^{13} , $P(0)R^{13}$, $p^{+}R^{13}R^{14}A$ -, phenylene, amino acid, replaced by 0, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO₂, $S^+R^{13}A^$ polyalkyl, peptide, polypeptide, carbohydrate, polyether, or wherein in RX, one or more carbons are optionally

S, SO, SO₂, S⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(O)R⁹; carbons are optionally replaced by 0, NR^9 , $N^+R^9R^{10}A^$ peptide, polypeptide, and carbohydrate, one or more wherein quaternary heterocycle and quaternary wherein in said polyalkyl, phenylene, amino acid,

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20 ᅜ and $N^+R^9R^{11}R^{12}A^-$, or P(0)R13R14, P+R13R14R15A-, P(OR13)OR14, S+R13R14A-, ${\rm SO_{3}R^{13}}$, ${\rm NR^{13}OR^{14}}$, ${\rm NR^{13}NR^{14}R^{15}}$, ${\rm NO_{2}}$, ${\rm CO_{2}R^{13}}$, ${\rm CN}$, ${\rm OM_{2}}$ SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more

25 prodrug thereof. a pharmaceutically acceptable salt, solvate, or

wherein: Preferred compounds in this class are compounds

consisting of alkylarylalkyl, alkylheteroarylalkyl, R' is phenyl substituted with OR130; $\mathbf{R}^{\mathbf{1}\mathbf{3}\mathbf{6}}$ is independently selected from the group

21

alkylheterocyclylalkyl, and carboxyalkylaminocarbonylalkyl; and

Rith is optionally substituted with one or more groups selected from the group consisting of carboxy, quaternary heterocycle, quaternary heteroaryl, and

More preferred compounds in this class are compounds wherein:

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R³ is phenyl substituted with OR^{11s}; R^{13s} is alkylarylalkyl; and

R¹¹⁸ is optionally substituted with one or more groups selected from the group consisting of quaternary heterocycle and quaternary heteroaryl.

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Still more preferred in this class are compounds wherein:

 R^{s} is phenyl substituted with OR^{11s} ; R^{11s} is alkylphenylalkyl; and

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R^{11s} is optionally substituted with one or more groups selected from the group consisting of quaternary heterocycle and quaternary heteroaryl.

A third class of compounds of particular interst consists of those compounds of formula I wherein

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q is an integer from 1 to 4_1

n is an integer from 0 to 2;

30

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl,
alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,
dialkylamino, alkylthio, (polyalkyl)aryl, and

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cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁴R⁹R¹⁰R^WA⁻, SR⁹, S'R^{R¹⁰A⁻. P⁴R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, CO₂R⁹, CN, halogen, OXO, and CONR⁹R¹⁰,}

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A-, p⁺R⁹R¹⁰A-, or phenylene,

wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl,

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carboxyheteroaryl, carboxyheterocycle, carboxylalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or R¹ and R² taken together with the carbon to which

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they are attached form C,-C, cycloalkyl;

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R³ and R⁴ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, and SO₃R⁹, wherein R⁹ and R¹⁰ are as defined above; or

 $\rm R^3$ and $\rm R^4$ together form =0, =NOR 11 , =S, =NNR $^{11}\rm R^{12}$, =NR 9 , or =CR $^{11}\rm R^{12}$,

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wherein R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, CO₂R⁹, CW, halogen, oxo, and CONR⁹R¹⁰,

wherein ${\rm R}^9$ and ${\rm R}^{10}$ are as defined above, provided that both ${\rm R}^3$ and ${\rm R}^4$ cannot be OH, NH,, and SH, or

 ${
m R}^{11}$ and ${
m R}^{12}$ together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

 R^{5} is aryl substituted with one or more OR^{13b} , wherein R^{13b} is selected from the group

wherein R^{AAD} is selected from the group consisting of alkyl, alkenyl, alkylarylalkyl, polyatkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, alkylheteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, heterocycle, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, and quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

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R^{13b} is substituted with one or more groups selected from the group consisting of carboxyalkyl, heterocycle, heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, or guanidinyl, and

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 R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(0)R^9$, SO_2R^9 , and SO_3R^9 ,

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wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heterocycle, can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle,

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quaternary heteroary1, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(0)NR¹³R¹⁴,

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C(0)0M, COR¹³, NR¹³C(0)R¹⁴, NR¹³C(0)RR¹⁴, NR¹³CO₂R¹⁴, NR¹³SO₃R¹⁴, NR¹³SO₄R¹⁴, NR¹³SO₄R¹⁴, NR¹³SO₄R¹⁴, P(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻,

wherei

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, said alkyl, alkenyl, alkynyl, polyalkyl,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, SO₃R⁷, CO₂R⁷, CN, OXO, CONR⁷R⁸, N⁺R⁷R⁸R⁹A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(O)R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(O)(OR⁷)OR⁸, and

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, pR⁷, P(O)R⁷, P⁺R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heterocycle, heterocycle, heterocycle, heterocycle, heterocycle, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, and carboxyalkylaminocarbonylalkyl,

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wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR*, N*R*PR10A-, S, SO, SO2,

S⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A⁻, P(0)R³, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R¹³, R¹⁴, and R¹⁵ are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, heterocyclyjalkyl, quaternary heteroarylalkyl, guanidinyl, oR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, p⁺R⁹R¹⁰R¹¹A, and C(O)OM,

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wherein R^{16} and R^{17} are independently selected

from the substituents constituting R^9 and M_1 or R^{13} and R^{14} , together with the nitrogen atom to

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R¹¹ and R¹¹, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring, and R^{10} is selected from the group consisting of

20

alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylanterocycle, ammoniumalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkyl, alkylammoniumalkyl, and alkylammoniumalkyl, and

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 ${\rm R}^7$ and ${\rm R}^8$ are independently selected from the group consisting of hydrogen and alkyl; and

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one or more $R^{\rm X}$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, eryl, arylalkyl, halogen,

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haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, oR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)₂R¹³, SO₃R¹³, S⁺R¹³R¹⁴A⁻, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C(O)R¹³, C(O)NR¹³R¹⁴, NR₁₄C(O)R₁₃, C(O)NR¹³R¹⁴, NR₁₄C(O)R₁₃, C(O)NR¹³R¹⁴, NR¹⁴G(O)R¹³, OR¹⁸, S(O)_{NNR}R¹⁸, NR¹⁸OR¹⁴, N⁺P⁸R¹¹R¹²A⁻, p⁺R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

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wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁴R⁹R¹¹R¹²A², SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁴)OR¹⁷, p⁴R⁹R¹¹R¹²A², S⁴R⁹R¹⁰A², or C(0)OM, and

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wherein \mathbb{R}^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

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wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and C(O)OM,

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wherein in R^X, one or more carbons are optionally replaced by O, ${\rm NR}^{13}$, ${\rm N}^+{\rm R}^{13}{\rm R}^{14}{\rm A}_-$, S, SO, SO₂, ${\rm S}^+{\rm R}^{13}{\rm A}^-$, PR¹³, P(0)R¹³, P⁺R¹³R¹⁴A⁻, phenylene, amino acid,

peptide, polypeptide, carbohydrate, polyether, or

s, so, so₂, s[†]R⁹A-, pR⁹, p[†]R⁹R¹⁰A-, or P(O)R⁹; carbons are optionally replaced by 0, NR, N+R,R10Apeptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

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 $503R^{13}$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OMSO20M, SO2NR13R14, C(O)NR13R14, C(O)OM, COR13 halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

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and N+R9R11R12A-, or P(0)R13R14, P+R13R14R15A-, P(OR13)OR14, S+R13R14Aa pharmaceutically acceptable salt, solvate, or

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wherein: Preferred compounds in this class are compounds

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prodrug thereof

quaternary heterocyclylalkyl; and consisting of alkyl, quaternary heteroarylalkyl, and R⁵ is phenyl substituted with OR¹³⁵; R^{110} is independently selected from the group

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selected from the group consisting of heterocycle, heteroaryl, and guanidinyl. R^{110} is substituted with one or more groups

consists of those compounds of formula I wherein q is an integer from 1 to 4; A fourth class of compounds of particular interest

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and R^2 are independently selected from the

n is an integer from 0 to 2;

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dialkylamino, alkylthio, (polyalkyl)aryl, and haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, group consisting of H, alkyl, alkenyl, alkynyl,

CONR⁹R¹⁰, OR9, NR9R10, N+R9R10RWA-, SR9, S'R'R'A-, P+R9R10R11A- $S(0)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, O(1), and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, substituents selected from the group consisting of cycloalkyl optionally are substituted with one or more dialkylamino, alkylthio, (polyalkyl)aryl, and wherein alkyl, alkenyl, alkynyl, haloalkyl

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optionally have one or more carbons replaced by O, phenylene, NR⁹, N⁺R⁹R¹⁰A-, s, so, so₂, s⁺R⁹A⁻, p⁺R⁹R¹⁰A⁻, or alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl wherein alkyl, alkenyl, alkynyl, alkylaryl, wherein R^9 , R^{10} , and R^W are independently

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heterocyclylalkyl, and alkylammoniumalkyl; or carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, carboxyheteroaryl, carboxyheterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, selected from the group consisting of H, alkyl,

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they are attached form C₁-C₁₀ cycloalkyl; \mathbb{R}^1 and \mathbb{R}^2 taken together with the carbon to which

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SO2R⁹, and SO3R⁹, wherein R' and R' are as defined group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, oR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, ${ t R}^3$ and ${ t R}^4$ are independently selected from the

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-NNR 11R 12, -NR 9, or -CR 11R 12 R³ and R⁴ together form =0, =NOR¹¹, =s,

wherein R^9 and R^{10} are as defined above, provided that alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, 302R⁹, SO3R⁹, CO2R⁹, CN, halogen, oxo, and CONR⁹R¹⁰, wherein R¹¹ and R¹² are independently selected rycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, from the group consisting of H, alkyl, alkenyl, neterocycle, carboxyalkyl, carboalkoxyalkyl, both R³ and R⁴ cannot be OH, NH,, and SH, or

S

 ${\bf R}^{11}$ and ${\bf R}^{12}$ together with the nitrogen or carbon atom to which they are attached form a cyclic ring,

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R⁵ is aryl substituted with one or more OR^{13b},

neterocycle, quaternary heteroaryl, heterocyclylalkyl, consisting of alkyl, alkenyl, alkynyl, polyalkyl, ycloalkyl, heterocycle, heteroaryl, quaternary heteroarylalkyl, quaternary heterocyclylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, wherein R^{13b} is selected from the group polyether, aryl, arylalkyl, alkylarylalkyl, quatermary heteroarylalkyl, alkoxyalkyl, carboxyalkylaminocarbonylalkyl, alkylammoniumalkyl, and

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N*R98R11R12A-, SR98, S(0)R98, SO2R98, SO3R98, CO2R98, CONR 9 BR 10, SO2NR 9 BR 10, P R 9 BR 10 R 11 A -, and S + R 9 BR 10 A -, selected from the group consisting of ${\rm OR}^{9a}$, ${\rm NR}^{9a}{\rm R}^{10}$, \mathbb{R}^{13b} is substituted with one or more groups

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anion and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable

wherein R⁹⁸ is selected from the group consisting carboxyalkylamino and carboxyalkylaminoalkyl, carboxyheterocycle, carboalkoxyalkyl, of carboxyalkyl, carboxyheteroaryl,

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R⁶ is selected from the group consisting of H, heterocycle, quaternary heterocycle, $0 \mathrm{R}^{30}$, SR^9 , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, S(0)R⁹, SO₂R⁹, and SO₃R⁹,

cycloalkyl, heterocycle, quaternary heterocycle, and SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, quaternary heteroaryl can be substituted with one or NO2, \cos^{13} , CN, OM, \cos_2 OM, \cos_2 NR 13 R 14 , C(O)NR 13 R 14 , more substituent groups independently selected from OC(0)R11, OC(0)NR11R14, NR11SOR14, NR11SO₂R14, NR11SONR14R18 NR11502NR14R15, P(0)R13R14, P+R13R14R15A, P(OR13)OR14 quaternary heteroaryl, halogen, oxo, OR 13 , NR 13 R 14 , C(0) OM, COR¹³, NR¹¹C(0) R¹⁴, NR¹¹C(0) NR¹⁴R¹⁸, NR¹¹CO₂R¹⁴, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkynyl, heterocycle, arylalkyl, quaternary heterocycle, wherein alkyl, alkenyl, alkynyl, aryl,

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S+R13R14A-, and N+R9R11R12A-,

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wherein:

A is a pharmaceutically acceptable anion and M consisting of OR7, NR7R, SR7, S(0)R7, SO2R7, SO3R7, COR7, CN, OXO, CONR7R8, N*R7R8R9A-, alkyl, alkenyl, heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, nore substituent groups selected from the group juaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and is a pharmaceutically acceptable cation, 20 25

wherein said alkyl, alkenyl, alkynyl, polyalkyl, P(0)R7R8, P+R7R8R9A-, and P(0) (OR7)OR8, and polyether, aryl, haloalkyl, cycloalkyl, and

of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, carboxyalkylaminocarbonylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary alkylheteroarylalkyl, alkylheterocyclylalkyl, are independently selected from the group consisting P(0)R⁷, P[†]R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ replaced by 0, NR⁷, N⁺R⁷R⁸A⁻, s, s0, s0₂, s⁺R⁷A⁻, PR^{7} heterocycle can optionally have one or more carbons alkylammoniumalkyl, and quaternary heteroarylalkyl, alkoxyalkyl, heterocycle, quaternary heteroaryl, heterocyclylalkyl, polyether, aryl, arylalkyl, alkylarylalkyl,

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S⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A-, P(O)R⁹, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and carbons replaced by O, NR, N+R,R10A-, S, SO, SO2, heterocycle, and polyalkyl optionally have one or more wherein alkyl, alkenyl, alkynyl, arylalkyl,

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CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R¹¹A , SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, heteroarylalkyl, guanidinyl, oR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²Aquaternary heterocyclylalkyl, quaternary quaternary heterocycle, quaternary heteroaryl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, of hydroxy, amino, sulfo, carboxy, alkyl, one or more groups selected from the group consisting $s^+ R^9 R^{10} A^-$, and C(0) OM, $^{
m R^{13}}$, $^{
m R^{14}}$, and $^{
m R^{15}}$ are optionally substituted with

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which they are attached form a mono- or polycyclic from the substituents constituting R9 and M; or R^{13} and R^{14} , together with the nitrogen atom to wherein R^{16} and R^{17} are independently selected

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oxo, carboxy and quaternary salts; or more radicals selected from the group consisting of heterocycle that is optionally substituted with one or

and alkylammoniumalkyl; and carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl carboxyheterocycle, carboalkoxyalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, which they are attached, form a cyclic ring; and ${{ t R}^{14}}$ and ${{ t R}^{15}}$, together with the nitrogen atom to R is selected from the group consisting of

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group consisting of hydrogen and alkyl; and ${\tt R}^7$ and ${\tt R}^8$ are independently selected from the

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 $p^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and S(0) nNR 18, NR 13 R 18, NR 18 OR 14, N+R 9 R 11 R 12 A-, $C(0)NR^{13}R^{14}$, $NR^{14}C(0)R13$, C(0)OM, COR^{13} , OR^{18} SO3R13, S+R13R14A-, NR13OR14, NR13NR14R15, NO2, heteroaryl, OR13, NR13R14, SR13, S(O)R13, S(O)2R13, polyether, quaternary heterocycle, quaternary polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, the group consisting of H, alkyl, alkenyl, alkynyl, one or more $\mathbb{R}^{\mathbf{X}}$ are independently selected from 3 , CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C(O)R¹³,

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quaternary heteroaryl can be further substituted with or⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹ haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl wherein alkyl, alkenyl, alkynyl, cycloalkyl

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oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO2OM, SO₂NR⁹R¹⁰

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PO(OR'')OR'', P'R'9R'1'R'2A', S'R'9R'0A', or C(O)OM, and wherein R'18 is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

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wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heterocycl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁷R⁹R¹¹R¹²A-, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and C(O)OM,

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wherein in R^X, one or more carbons are optionally replaced by 0, NR¹³, N^{*}R¹³R¹⁴A₋, S, SO, SO₂, S^{*}R¹³A⁻, PR¹³, P(O)R¹³, P*R¹³R¹⁴A₋, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

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wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, S, SO, SO₂, S⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(O)R¹;

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wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, oR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, P(O)R¹³R¹⁴, P¹R¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴, S¹R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻, or

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a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferred compounds in this class are compounds

wherein:

R\$ is phenyl substituted with OR139;

 R^{138} is selected from the group consisting of alkyl and alkoxyalkyl; and

R¹¹⁹ is substituted with one or more groups selected from the group consisting of OR" and NR"R";

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R** is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, and carboxyheterocycle; and

R10 is carboxyalkyl.

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A fifth class of compounds of particular interest consists of those compounds of formula I wherein

q is an integer from 1 to 4; n is an integer from 0 to 2;

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R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

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wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^MA⁻, SR⁹, S'R^{*}R¹⁰A. p⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, Oxo, and

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wherein alkyl, alkenyl, alkynyl, alkylaryl,
alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl

NR9, N+R9R10A-, S, SO, SO2, S+R9A', P+R9R10A', or optionally have one or more carbons replaced by 0,

heterocyclylalkyl, and alkylammoniumalkyl; or carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyheteroaryl, carboxyheterocycle, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, selected from the group consisting of H, alkyl, ammoniumalkyl, arylalkyl, carboxyalkyl, \mathbb{R}^1 and \mathbb{R}^2 taken together with the carbon to which wherein R^9 , R^{10} , and R^W are independently

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they are attached form C₁-C₁₀ cycloalkyl;

SO2R⁹, and SO3R⁹, wherein R' and R' are as defined acyloxy, aryl, haterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, group consisting of H, alkyl, alkenyl, alkynyl, above; or and ${ t R}^{f 4}$ are independently selected from the

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"NNR 11 R 12, "NR 9, or "CR 11 R 12 \mathbb{R}^3 and \mathbb{R}^4 together form =0, =NOR 11 , =S

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 $\mathrm{SO_2R}^9$, $\mathrm{SO_3R}^9$, $\mathrm{CO_2R}^9$, CN, halogen, oxo, and $\mathrm{CONR}^9\mathrm{R}^{10}$, both R^3 and R^4 cannot be OH, NH₃, and SH, or wherein ${ t R}^9$ and ${ t R}^{10}$ are as defined above, provided that cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, heterocycle, carboxyalkyl, carboalkoxyalkyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, from the group consisting of H, alkyl, alkenyl, wherein R^{11} and R^{12} are independently selected

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atom to which they are attached form a cyclic ring; $m R^{11}$ and $m R^{12}$ together with the nitrogen or carbon wherein $R^{f 13b}$ is selected from the group R⁵ is aryl substituted with one or more OR 13b,

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carboxyalkylaminocarbonylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and heteroarylalkyl, quaternary heterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, consisting of alkyl, alkenyl, alkynyl, polyalkyl,

SO2NR9R10a, P+R9R10aR11A-, and S+R9R10aA-, carboxyalkylheterocyclyl, NR⁹R^{10a}, CONR⁹R^{10a} selected from the group consisting of $^{
m R}^{
m 13b}$ is substituted with one or more groups

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anion and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable

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heterocyclylalkyl; or consisting of carboxyalkyl, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, and wherein \mathbb{R}^{10a} is selected from the group

 $s(0)R^9$, so_2R^9 , and so_3R^9 , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, ${ t R}^6$ is selected from the group consisting of H,

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heterocycle, arylalkyl, quaternary heterocycle, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkynyl, quaternary heteroaryl can be substituted with one or more substituent groups independently selected from cycloalkyl, heterocycle, quaternary heterocycle, and wherein alkyl, alkenyl, alkynyl, aryl,

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 NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$ SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵ quaternary heteroaryl, halogen, oxo, OR¹³, NR¹³R¹⁴

OC(0) R11, OC(0) NR13R14, NR13SOR14, NR13SO2R14, NR13SONR14R18 NR13SO,NR14R15, P(O)R13R14, P*R13R14R15A-, P(OR13)OR14 C(0) OM, COR^{13} , $NR^{13}C(0)R^{14}$, $NR^{13}C(0)NR^{14}R^{15}$, $NR^{13}CO_3R^{14}$, S*R13R14A-, and N*R9R11R12A-,

wherein:

S

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

consisting of OR7, NR7R8, SR7, S(O)R7, SO2R7, SO3R7, CO2R7, CN, oxo, CONR7R8, N+R7RBR9A-, alkyl, alkenyl, heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, nore substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and P(0)R7R8, P+R7R8R9A-, and P(0) (OR7)OR8, and

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neterocycle, quaternary heteroaryl, heterocyclylalkyl, replaced by O, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R7, P+R7RBA-, or phenylene, and R13, R14, and R15 wherein said alkyl, alkenyl, alkynyl, polyalkyl, are independently selected from the group consisting heterocycle can optionally have one or more carbons quaternary heteroarylalkyl, alkylammoniumalkyl, and of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, sycloalkyl, heterocycle, heteroaryl, quaternary neteroarylalkyl, quaternary heterocyclylalkyl, lkylheteroarylalkyl, alkylheterocyclylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and polyether, aryl, arylalkyl, alkylarylalkyl, :arboxyalkylaminocarbonylalkyl,

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heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', N⁺R⁹R¹⁰A-, S, SO, SO₂, wherein alkyl, alkenyl, alkynyl, arylalkyl,

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carbohydrate, amino acid, peptide, or polypeptide, and s*R9A', PR9, p*R9R10A-, P(0)R', phenylene,

 R^{13} , R^{14} , and R^{15} are optionally substituted with CONR 9R 10, SO2OM, SO2NR 9R 10, PO(OR 16)OR 17, P + R 9R 10R 11Aheteroarylalkyl, guanidinyl, OR 9 , NR 9 R 10 , N $^+$ R 9 R 11 R 1 A $^$ one or more groups selected from the group consisting , SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quatermary heterocycle, quatermary heteroaryl, quaternary heterocyclylalkyl, quaternary of hydroxy, amino, sulfo, carboxy, alkyl, S*R9R10A-, and C(O)OM,

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wherein R^{16} and R^{17} are independently selected from the substituents constituting R9 and M; or

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heterocycle that is optionally substituted with one or more radicals selected from the group consisting of R" and R", together with the nitrogen atom to which they are attached form a mono- or polycyclic oxo, carboxy and quaternary salts; or

 R^{14} and R^{15} , together with the nitrogen atom to R is selected from the group consisting of which they are attached, form a cyclic ring; and

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carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, and alkylammoniumalkyl, and

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 ${\bf R}^7$ and ${\bf R}^8$ are independently selected from the group consisting of hydrogen and alkyl; and

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one or more \mathbb{R}^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen,

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haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heterocycle, quaternary heterocycle, quaternary heterocycle, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, S(0)R¹³, S(0)R¹³, S(0)₂R¹³, S(0)₂R¹³, S(0)₂R¹³, NR¹³A₁, NR¹³OR¹⁴, NR¹³R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C(0)R¹³, OR¹⁸, C(0)NR¹³R¹⁴, NR¹⁴C(0)R13, C(0)OM, COR¹³, OR¹⁸, S(0)₁NR¹⁸, NR¹³R¹⁸; NR¹⁸OR¹⁴, N*_R⁹R¹¹R¹²A⁻, P*R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

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wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹¹) OR¹¹, P⁺R⁹R¹¹R¹²A⁻, S⁺R⁹R¹⁰A⁻, or C(0)OM, and

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wherein ${\bf R}^{18}$ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

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wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N+R⁹R¹¹R¹²A-, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and C(O)OM,

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wherein in R^X , one or more carbons are optionally replaced by 0, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO₂, $S^+R^{13}A^-$, PR^{13} , $P(0)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid,

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peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, S, SO, SO₂, S⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(O)R⁹; wherein quaternary heterocycle and quaternary

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂OR SO₂

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and $N^{+}R^{2}R^{11}R^{12}A^{-}$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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20 Preferred compounds in this class are compounds wherein:

R¹¹⁰ is alkyl; and
R¹¹⁰ is substituted with OR¹¹⁰,
R¹¹⁰ is substituted with NR¹⁰⁰; and
R¹ is hydrogen; and
R¹⁰ is heteroarylalkyl.

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A sixth class of compounds of particular interest consists of those compounds of formula I wherein

q is an integer from 1 to 4; n is an integer from 0 to 2;

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 \mathbb{R}^1 and \mathbb{R}^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

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haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of or⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^WA⁻, SR⁹, S'R^{*}R¹⁹A⁻. p⁺R⁹R¹⁰R¹¹A⁻, S(0)R⁹, SO₂R⁹, SO₂R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

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wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A', p⁺R⁹R¹⁰A', or phenylene,

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wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheterocycle, carboxyheterocycle, carboxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

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 $\rm R^1$ and $\rm R^2$ taken together with the carbon to which they are attached form C,-C,0 cycloalkyl,

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R³ and R⁴ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, and SO₃R⁹, wherein R⁸ and R¹⁰ are as defined above; or

 $\rm R^3$ and $\rm R^4$ together form =0, =NOR 11 , =S, =NNR $^{11}\rm R^{12}$, =NR 9 , or =CR $^{11}\rm R^{12}$,

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wherein R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, SO3R⁹, CO2R⁹, CN, halogen, oxo, and CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above, provided that

 $\rm R^{11}$ and $\rm R^{12}$ together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

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both R³ and R⁴ cannot be OH, NH₂, and SH, or

R⁵ is aryl substituted with one or more substituent groups independently selected from the group consisting of NR¹²C(O)R¹⁴, NR¹⁵C(O)R¹⁴, NR¹⁴C(O)R¹⁴, NR¹⁵CO₁R¹⁴, NR¹⁵CO₁R¹⁵, NR¹⁵CO₁R¹⁵CO₁R¹⁵, NR¹⁵CO₁R¹

wherein:

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R13, R14, and R15 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycly, quaternary heterocycl, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary carboxyalkylaminocarbonylalkyl,

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R13, R14, and R15 are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heterocycly, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary

, sr⁹, s(0) r⁹, so₂ r⁹, so₃ r⁹, oxo, co₂ r⁹, cN, halogen, conr⁹ r¹⁰, so₂om, so₂ nr⁹ r¹⁰, po (or¹⁶) or¹⁷, p⁺ r⁹ r¹⁰ r¹¹ a, s⁺ r⁹ r¹⁰ a⁻, and c(0) om,

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, wherein R¹⁶ and R¹⁷ are independently selected from the substituents constituting R⁹ and M; or R¹¹ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of

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oxo, carboxy and quaternary salts; or \mathbb{R}^{14} and \mathbb{R}^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R⁶ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹,

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wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heterocycle, and quaternary heterocycle, and quaternary heterocycle, and the substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, arylalkyl, functionary heterocycle, arylalkyl, guaternary heterocycle, spl3, s02R13, s02R13, NR13R14, NR13R14, SC10) ox, co2R13, CN, om, s02OM, s02NR13R14, C(0)NR13R14, C(0)OM, COR13, NR14C(0)R14, NR15OR14, N

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stR13R14A-, and NtR9R11R12A-, wherein:

A is a pharmaceutically acceptable anion and M
is a pharmaceutically acceptable cation,
said alkyl, alkenyl, alkynyl, polyalkyl,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(0)R⁷, SO₂R⁷, SO₃R⁷, CO₂R⁷, CN, OXO, CONR⁷R⁸, N⁺R⁷R⁸R⁹A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(0)R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(0) (OR⁷)OR⁸, and

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ผ 20 15 carboxyalkylaminocarbonylalkyl, of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and heterocycle, quaternary heteroaryl, heterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary alkylheteroarylalkyl, alkylheterocyclylalkyl, are independently selected from the group consisting $P(0)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} replaced by 0, NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7 polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons wherein said alkyl, alkenyl, alkynyl, polyalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR*, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A-, P(O)R⁹, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and R¹³, R¹⁴, and R¹⁵ are optionally substituted with

one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, guanidinyl, oR⁹, NR⁹Rl⁰, N⁺R⁹Rl¹Rl²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹Rl⁰, SO₂OM, SO₂NR⁹Rl⁰, PO(ORl⁶)ORl⁷, P⁺R⁹Rl⁰Rl¹A-, and C(O)OM,

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wherein R¹⁶ and R¹⁷ are independently gelected from the substituents constituting R⁹ and M; or R¹³ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

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R¹⁴ and R¹⁵, together with the nitrogen atom to which they are attached, form a cyclic ring; and R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkyl, and alkylammoniumalkyl; and

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 $\ensuremath{\mathrm{R}}^7$ and $\ensuremath{\mathrm{R}}^8$ are independently selected from the group consisting of hydrogen and alkyl; and

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one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)R¹³,

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SO3R¹³, S⁺R¹³R¹⁴A₋, NR¹³OR¹⁴, NR¹³UR¹⁴R¹⁵, NO₂, CO₂R¹³, CM, OM, SO₂OM, SO₂UR¹³R¹⁴, NR¹⁴C(O)R¹³, C(O)NR¹³R¹⁴, NR₁₄C(O)R₁₃, C(O)OM, COR¹³, OR¹⁸, S(O)_DUR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺8⁹R¹¹R¹²A⁻, $p^+ R^2 R^{11} R^{12} A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹Rl⁰, N⁺R⁹Rl¹Rl²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹Rl⁰, SO₂OM, SO₂NR⁹Rl⁰, PO (OR¹¹)OR¹⁷, P⁺R⁹Rl¹Rl²A⁻, S⁺R⁹Rl⁰A⁻, or C(O)OM, and

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wherein \mathbb{R}^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

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wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and C(O)OM,

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wherein in R^{X} , one or more carbons are optionally replaced by 0, NR^{13} , $N^{+}R^{13}R^{14}A^{-}$, S, SO, SO₂, $S^{+}R^{13}A^{-}$, PR^{13} , $P(0)R^{13}$, $P^{+}R^{13}R^{14}A^{-}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

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wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more

s, so, so₂, s⁺R⁹A-, pR⁹, p⁺R⁹R¹⁰A-, or P(0)R⁹; carbons are optionally replaced by O, NR⁹, N[†]R⁹R¹⁰A

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and N+R9R11R12A-, or P(0)R13R14, P+R13R14R15A-, P(OR13)OR14, S+R13R14A- SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , groups selected from the group consisting of alkyl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, heteroaryl are optionally substituted with one or more a pharmaceutically acceptable salt, solvate, or wherein quaternary heterocycle and quaternary

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prodrug thereof.

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wherein: Preferred compounds in this class are compounds

from the group consisting of NR12(0)NR181 and NR12CO,R11 R^s is aryl substituted with a radical selected

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from the group consisting of NR11C(0)NR14R15 and NR11CO,R14 compounds wherein: R's is phenyl substituted with a radical selected

More preferred compounds

In this class are

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the following conditions exist: the above embodiments, wherein at least one or more of directed to compounds of Formula I, including each of Other embodiments of the invention are further

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group consisting of hydrogen and alkyl. Preferably, R consisting of C1., alkyl. More preferably, R1 and R2 are and R² are independently selected from the group the same C., alkyl. (1) R' and R' are independently selected from the Still more preferably, R and R

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are n-butyl, and/or

- and R' is OR". Still more preferably, R' is hydrogen group consisting of hydrogen and OR' wherein R' is and R' is hydroxy; and/or defined as set forth above. (2) R' and R' are independently selected from the Preferably, R' is hydrogen
- quaternary heteroaryl or substituted amino; and/or substituted at the para or meta position with OR11 with OR". above. Still more preferably, R' is phenyl substituted and NR¹³SO₂NR¹⁴R¹⁴ wherein R¹³, R¹⁴ and R¹⁵ are as set forth OC(O)R", OC(O)NR"R", NR"SOR", NR"SO,R", NR"SONR"R" consisting of OR11, NR12C(O)R14, NR12C(O)NR14R11, NR12CO,R14 substituted with a radical selected from the group substituted phenyl. wherein R" (3) R' is substituted aryl. Preferably, R' is SEIII comprises a quaternary heterocycle, more preferably, R More preferably, R' is phenyl is phenyl

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(4) R' is hydrogen; and/or

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- group consisting of hydrogen and alkyl. Preferably, R' preferably, R' and R' are hydrogen; and/or consisting of hydrogen and C1.4 alkyl. and R' are independently selected from the group (5) R' and R' are independently selected from the Still more
- (6) R is selected from the group consisting of

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dimethylamino. dialkylamino. Still more preferably, R* is selected and NR¹¹R¹⁴. Preferably, R[#] is selected from the group consisting of alkoxy, amino, alkylamino and from the group consisting of methoxy and

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selected from among: The invention is further directed to a compound

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alkyne diyl, polyalkane diyl, alkoxy diyl, polyether consisting of alkane diyl, alkene diyl, alkyne diyl, nore carbon atoms replaced by O, NR⁷, N⁺R⁷R⁸, S, SO, peptide, and polypeptide can optionally have one or polyalkoxy dlyl, carbohydrate, amino acid, peptide, and polypeptide, wherein alkane diyl, alkene diyl, quatarnary heterocycle, quaternary heteroaryl, or SO2, S⁺R⁷R⁸, PR⁷, P⁺R⁷R⁸, phenylene, heterocycle, diyl, polyalkoxy diyl, carbohydrate, amino acid, wherein R19 is selected from the group polyalkane diyl, alkoxy diyl, polyether diyl,

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SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, heterocycle, arylalkyl, halogen, oxo, OR 13 , NR 13 R 14 , 102, \cos^{13} , CN, OM, \cos_2 OM, \cos_2 NR 13 R 14 , C(O)NR 13 R 14 , and polypeptide can be substituted with one or more polyalkoxy diyl, carbohydrate, amino acid, peptide, wherein alkane diyl, alkene diyl, alkyne diyl, substituent groups independently selected from the oolyalkyl, polyether, aryl, haloalkyl, cycloalkyl, polyalkane diyl, alkoxy diyl, polyether diyl, group consisting of alkyl, alkenyl, alkynyl,

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C(0) OM, COR¹³, P(0) R¹³R¹⁴, P⁺R¹³R¹⁴R15A-, P(OR¹¹) OR¹⁴, S'R11R1A', and N'R9R11R12A-,

R2 comprises a benzothiepine moiety as described above compounds of Formula DIII. Each of R20, R21, or R22 and wherein R19 further comprises functional linkages that is therapeutically effective in inhibiting ileal compounds of Formulae DII and DIII, and R23 in the by which R19 is bonded to R20, R21, or R22 in the

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comprises a benzothiepine molety corresponding to the The invention is also directed to a compound Formula DIII in which each of R20, R21, R22 and R21 selected from among Formula DI, Formula DII and Formula:

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(Formula DIV)

or:

wherein R', R', R', R', R', R', R", R", g, and n are

either a covalent bond or arylene. as defined in Formula I as described above, and R55 is 51

moiety bonded at a m- or p-carbon thereof to R1. and DIII, and R^{23} in Formula DIII, be bonded at its 7-or 8-position to R^{19} . In compounds of Formula DIVA, it is particularly preferred that R comprise a phenylene preferred that each of R20, R21, and R22 in Formulae DII In compounds of Formula DIV, it is particularly

Examples of Formula DI include:

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$$\begin{bmatrix} O + A & R^{1} & R^{2} & R^$$

and

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CH₃SO₃

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discussed immediately above, benzothiepine compounds In any of the dimeric or multimeric structures of the present invention can be used alone or in various combinations.

In any of the compounds of the present invention, R' and R' can be ethyl/butyl or butyl/butyl.

Another class of compounds of interest includes the following compounds:

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5 diluent. pharmaceutically acceptable carrier, excipient, or thereof across digestive system membranes, and a of the compounds disclosed above, alone or in treatment of a disease or condition for which a bile a pharmaceutical composition for the prophylaxis or acid levels in the blood, or to reduce transport combination, in an amount effective to reduce bile atherosclerosis. Such compositions may comprise any hyperlipidemic condition, for example, acid transport inhibitor is indicated, such as a In another aspect, the present invention provides

an effective amount in unit dosage form or in divided compounds disclosed above, alone or in combination, in administering to a patient in need any of the transport inhibitor is indicated, comprising in mammals, including humans, for which a bile acid provides a method of treating a disease or condition In a further aspect, the present invention also

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a medicament for use in treating a disease or provides the use of any of the compounds disclosed above, alone or in combination, in the preparation of In a further aspect, the present invention also

and

condition in mammals, including humans, for which a bile acid transport inhibitor is indicated.

In yet a further aspect, the present invention compounds of the present invention as discussed in also provides processes for the preparation of greater detail below.

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understood that the following detailed description and spirit and scope of the invention will become apparent Further scope of the applicability of the present the invention, are given by way of illustration only examples, while indicating preferred embodiments of description provided below. However, it should be since various changes and modifications within the invention will become apparent from the detailed to those skilled in the art from this detailed lescription.

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DETAILED DESCRIPTION OF THE INVENTION

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The following detailed description is provided to not be construed to unduly limit the present invention ild those skilled in the art in practicing the present invention. Even so, this detailed description should skill in the art without departing from the spirit or is modifications and variations in the emobodiments discussed herein can be made by those of ordinary scope of the present inventive discovery.

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herein, including the contents of the references cited The contents of each of the references cited incorporated by reference in their entirety. dthin these primary references, are herein

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Definitions

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In order to aid the reader in understanding the collowing detailed description, the following

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definitions are provided:

alkyl or two to twenty carbons for alkenyl and alkynyl example, methyl, ethyl, propyl, butyl, pentyl or hexyl chain hydrocarbons of from one to twenty carbons for and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl otherwise noted are each straight chain or branched in the present invention and therefore mean, for "Alkyl", "alkenyl," and "alkynyl" unless respectively and isomers thereof.

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"Aryl" means a fully unsaturated mono- or multisubstituted or unsubstituted phenyl, naphthyl, or ring carbocyle, including, but not limited to, anthracenyl.

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carbon atoms can be replaced by N, S, P, or O. This "Heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more includes, for example, the following structures:

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wherein Z, Z', Z" or Z" ' is C, S, P, O, or N, with substituents are understood to be attached to Z, Z', ç the proviso that one of Z, Z', Z" or Z" ' is other unother 2 atom by a double bond or when attached than carbon, but is not 0 or S when attached to another 0 or S atom. Furthermore, the optional Z" or Z" ' only when each is C.

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The term "heteroaryl" means a fully unsaturated heterocycle.

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point of attachment to the molecule of interest can be In either "heterocycle" or "heteroaryl," the

molecule of interest can be at a heteroatom or that it is positively charged. The point of at the heteroatom or elsewhere within the ring attachment of the quaternary heterocycle to the heterocycle in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds The term "quaternary heterocycle" means a

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elsewhere. molecule of interest can be at a heteroatom or attachment of the quaternary heteryaryl to the that it is positively charged. The point of heteroaryl in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds The term "quaternary heteroary1" means a

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or iodo group. The term "halogen" means a fluoro, chloro, bromo 15

with one or more halogens. The term "haloalkyl" means alkyl substituted

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the benzothiepine. common with the seven-membered heterocyclic ring of cyclohexyl, cycloalkenyl, and cycloheptyl. The term wherein the cycloalkyl ring has a carbon ring atom in radicals such as cyclopropyl, cyclobutyl, cyclopentyl, or more double or triple bonds. Examples include ten carbon atoms, and wherein any ring can contain one ringed carbocycle wherein each ring contains three to cycloalkyl additionally encompasses spiro systems The term "cycloalkyl" means a mono- or multi-

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said moiety has two points of attachment to molecules The term "diyl" means a diradical moiety wherein

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up to about 20,000, more preferably up to about straight hydrocarbon chain having a molecular weight The term "polyalkyl" means a branched or The term "oxo" means a doubly bonded oxygen.

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10,000, most preferably up to about 5,000.

the polyether has a molecular weight up to about one or more carbons are replaced by oxygen, wherein preferably up to about 5,000. 20,000, more preferably up to about 10,000, most The term "polyether" means a polyalkyl wherein

up to about 10,000, most preferably up to about 5,000. molecular weight up to about 20,000, more preferably alkylene oxides, wherein the polyalkoxy has a The term "polyalkoxy" means a polymer of

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not within the ring structures. ring structure is doubly bonded to an atom which is multi-ringed carbocycle wherein a carbon within the The term "cycloalkylidene" means a mono- or

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example, hydroxypropyl-methylcellulose or chitosan. have a molecular weight of up to about 20,000, for , or polysaccharide wherein the polysaccharide can The term " carbohydrate" means a mono-, di-, tri-

containing up to about 100 amino acid units. The term "peptide" means polyamino acid

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preferably from about 100 amino acid units to about 500 amino acid units. amino acid units to about 750 amino acid untis, most 1000 amino acid units, more preferably from about 100 containing from about 100 amino acid units to about The term "polypeptide" means polyamino acid

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bonded to the molecule of interest. which is bonded to an alkyl wherein said alkyl is or a mono-, di- or tri-substituted amino group, any of The term "alkylammoniumalkyl" means a NH, group

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which isomers are possible, such isomers are included which contain more than one ring heteroatom and for in the definition of said heterocycles and isomers. In all other heterocycles and heteroaryls The term "triazolyl" includes all positional

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The term "sulfo" means a sulfo group, -SO,H, or its salts.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

The term "arylalkyl" means an aryl-substituted alkyl radical such as benzyl. The term "alkylarylalkyl" means an arylalkyl radical that is substituted on the aryl group with one or more alkyl groups.

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The term "heterocyclylalkyl" means an alkyl radical that is substituted with one or more heterocycle groups. Preferable heterocyclylalkyl radicals are "lower heterocyclylalkyl" radicals having one or more heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

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The term "heteroarylalkyl" means an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one or more heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

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The term "quaternary heterocyclylalkyl" means an alkyl radical that is substituted with one or more quaternary heterocycle groups. Preferable quaternary heterocyclylalkyl radicals are "lower quaternary heterocyclylalkyl" radicals having one or more quaternary heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

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The term "quaternary heteroarylalkyl" means an alkyl radical that is substituted with one or more quaternary heteroaryl groups. Preferable quaternary heteroarylalkyl radicals are "lower quaternary heteroarylalkyl" radicals having one or more quaternary heteroaryl groups attached to an alkyl

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radical having one to ten carbon atoms.

The term "alkylheteroarylalkyl" means a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are "lower alkylheteroarylalkyl" radicals with alkyl portions having one to ten carbon atoms.

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The term "alkoxy" an alkyl radical which is attached to the remainder of the molecule by oxygen, such as a methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and tert-butoxy.

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The term "carboxy" means the carboxy group, -CO₃H, or its salts.

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The term "carboxyalkyl" means an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are "lower carboxyalkyl" radicals having one or more carboxy groups attached to an alkyl radical having one to six carbon atoms.

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The term "carboxyheterocycle" means a heterocycle radical that is substituted with one or more carboxy groups.

The term "carboxyheteroaryl" means a heteroaryl radical that is substituted with one or more carboxy groups.

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The term "carboalkoxyalkyl" means an alkyl radical that is substituted with one or more alkoxycarbonyl groups. Preferable carboalkoxyalkyl radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical having one to six carbon atoms.

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The term "carboxyalkylamino" means an amino radical that is mono- or di-substituted with carboxyalkyl. Preferably, the carboxyalkyl

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substituent is a "lower carboxyalkyl" radical wherein the carboxy group is attached to an alkyl radical having one to six carbon atoms.

The term "active compound" means a compound of the present invention which inhibits transport of bile acids.

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When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

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The term "a bile acid transport inhibitor" means a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

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Compounds

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The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

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Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the compounds of the present invention.

The compounds of the present invention also

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include tautomers.

The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

Compound Syntheses

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The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

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Generally, the compounds of the present invention can be prepared by the procedures described below.

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gives isomeric sulfone-epoxides IX which upon 3 equivalents of m-chloro-perbenzoic acid (MCPBA) give a mixture of 2,3-dihydrobenzothiepine VII and two benzothiepine-1,1-dioxides XI when R1 and R2 are hydrogenation with palladium on carbon as the catalyst and two racemic stereoisomers of 2,3,4,5-tetrahydrohydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides x yield a mixture of four racemic stereoisomers of 4when R^1 and R^2 are nonequivalent. Oxidation of VII with racemic steroisomers of benzothiepin-(5H)-4-one VIII yields keto-aldehyde VI which can be cyclized with the in WO 93/16055, in the presence of triethylamine with thiophenol V, prepared by the procedure described in refluxing ethylene glycol dimethyl ether (DME), to reagent, prepared from zinc and titanium trichloride Chem. Ber. 98, 728-734 (1965). Reaction of mesylate IV triethylamine similar to the procedure described in mesylate IV with methansulfonyl chloride and yields the hydroxyaldehyde III which is converted to aldehyde II with formaldehyde and sodium hydroxide For example, as shown in Scheme I, reaction of

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Optically active compounds of the present

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as described in J. Org. Chem., 39, 3904 (1974), ibid., starting material III or by resolution of compounds X with optical resolution agents well known in the art invention can be prepared by using optically active 42, 2781 (1977), and ibid., 44, 4891 (1979).

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$$A \xrightarrow{Z_{N} \cap \Gamma \cap J_{3}} \bigotimes_{(R^{1})_{q}} \bigotimes_{(R$$

Alternatively, keto-aldehyde VI where R2 is H can be prepared by reaction of thiophenol V with a 2substituted acrolein.

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also be carried out with potassium t-butoxide in THF. phase transfer catalyst (PTC). The transformation can with 40-50% sodium hydroxide in the presence of a XII which can be reduced with sodium borohydride to benzothiepine ring by reaction in methylene chloride $\mathbf{R}^{\mathbf{s}}$ on the opposite sides of the benzothiepine ring can give four racemic stereoisomers of X. The two MCPBA to give the benzothiepin-(5H)-4-one-1,1-dioxide Benzothiepin-(5H)-4-one VIII can be oxidized with having the OH group and R' on the same side of the be converted to the other two isomers of X, Xc and Xd, stereoisomers of X, Xa and Xb, having the OH group and

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reaction of epoxide IX where R' is H with thiol, NRR' and S(0),R and R' is hydroxy can be prepared by The compounds of the present invention where R' is OR, 6c = Xc &=X 6a = Xa when $R^1 = butyt$, $R^2 = ethyt$, $R^3 = phenyt$, X = H, q = 4PTC = phase transfer catalyst MCPBA = m-chloroperbenzoic acid

alcohol, and amine in the presence of a base.

R⁵ = OR, NRR', S(O),R

IX, where R⁵ = H

with palladium on carbon yields compound XIV which can Another route to Xc and Xd of the present invention is be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture chloroperbenzoic acid. Hydrogenolysis of compound XIII shown in Scheme 2. Compound VI is oxidized to of Xc and Xd. Separation of Xc and Xd can be accomplished by either HPLC or fractional compound XIII with two equivalent of mcrystallization.

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the thiophenol XVIII. Similarly, Thiophenol V can also invention can also be prepared according to the Scheme procedure in J. Chem. Soc., 2431-2432 (1958) gives the chermally rearranged at 200~300 °C, and the rearranged be prepared from 2-acylphenol XIX via the intermediate ortho substituted phenol XVI. The phenol XVI can be product is hydrolyzed with sodium hydroxide to yield org. Chem., 31, 3980 (1966). The phenol XVI is first hiocarbamate XVII by the procedure described in J. riethylamine to give thiocarbamate XVII which is reacted with dimethyl thiocarbamoyl chloride and chloride in a nonpolar solvent according to the The thiophenols XVIII and V used in the present . Alkylation of phenol XV with an arylmethyl converted to the thiophenol XVIII via the thiocarbamate XX.

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XVIII. Compound XVIII can be reacted with mesylate IV sulfide-aldehyde with potassium t-butoxide also gives 1,1-dioxides Xc and Xd starting from the thiophenol Scheme 4 shows another route to benzothiepinebutoxide to a mixture of Xc and Xd. Cyclyzation of to give the sulfide-aldehyde XXI. Oxidation of XXI aldehyde XIV which can be cyclized with potassium with two equivalents of MCPBA yields the sulfonea mixture of benzothiepine XXII

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sulfone-aldehyde XXIV which can be reduced by Oxidation of XXIII with 2 equivalents of MCPBA yields sulfide followed by reacting the resulting sulfide hydrogenation to the hydroxylamine XXV. Protecting the with mesylate IV gives sulfide-aldehyde XXIII. nitrodiphenylmethane 32. Reaction of 32 with lithium trifluoromethane sulfonic acid to 2-chloro-4nitrobenzophenone is reduced with triethylsilane and shown in Scheme 5 and Scheme 6. 2-Chloro-4compounds of the present invention can be prepared as Examples of amine- and hydroxylamine-containing

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hydrogenation of XXIV or XXVIIc and XXVIId. gives a mixture of hydroxylamino derivatives XXVIIc XXVI. Cyclization of XXVI with potassium t-butoxide derivatives can also be prepared by further and XXVIId. The primary amine XXXIIIc and XXXIIId and removal of the t-butoxycarbonyl protecting group N, O-di-(t-butoxycarbonyl) hydroxylamino derivative hydroxylamine XXV with di-t-butyldicarbonate gives the

aldehyde catalyzed by palladium on carbon in the same XXV with hydrogen followed by reductive alkylation of potassium t-butoxide yields a mixture of substituted the resulting amino derivative with hydrogen and an derivative XXVIII. Cyclization of XXVIII with reaction vessel yields the substituted amine

amino derivatives of this invention XXIXc and XXIXd.

PCT/US99/12828 Scheme 5

In Scheme 6, reduction of the sulfone-aldehyde

H₂ · Pd/C R°CH2OH

ZXX

potassium t-butoxide, THF

XXXX PXXXX

10 Hydrolysis of the carboxylate and derivatization of the 5 substituent to the aryl ring at the 5-position of resulting acid to acid derivatives are well known in the carbonylation in an alcohol yields the carboxylate XXXII. derivative XXXI, which upon palladium-catalyzed benzothiepine. Iodination of 5-phenyl derivative XXX with iodine catalyzed by mercuric triflate gives the iodo Scheme 7 describes one of the methods of introducing a

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80 Scheme 7

have the following meanings: Abbreviations used in the foregoing description

THF---tetrahydrofuran

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PTC---phase transfer catalyst

Aliquart 336---methyltricaprylylammonium chloride MCPBA---m-chloroperbenzoic acid

Celite--- a brand of diatomaceous earth filtering aid

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DMF---dimethylformamide

DME----ethylene glycol dimethyl ether

BOC---t-butoxycarbonyl group

4e---methyl

St---ethyl

3u---butyl

StOAc -- ethyl acetate Et,0---diethyl ether CH,Cl, --- methylene chloride

4gSO,---magnesium sulfate

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NaOH---sodium hydroxide

HCl --- hydrochloric acid CH,OH---methanol

NaCl---sodium chloride

LAH---lithium aluminum hydride NaH---sodium hydride

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LiOH---lithium hydroxide

NaHCO, --- sodium bicarbonate Na,SO, --- sodium sulfite

DMSO---dimethylaulfoxide

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KOSiMe, --- potassium trimethylsilanolate

PEG---polyethylene glycol

MS---mass spectrometry

HRMS---high resolution mass spectrometry ES---electrospray

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NMR---nuclear magnetic resonance spectroscopy

MPLC---medium pressure liquid chromatography GC---gas chromatography

RPHPLC---reverse phase high pressure liquid HPLC---high pressure liquid chromatography

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chromatography

RT---room temperature

h or hr --- hour (s)

min---minute (8)

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"Enantiomerically-enriched" (e.e.) means that one enantiomer or set of diastereomers preponderates over

the complementary enantiomer or set of diastereomers.

other enantiomer, multiplying the dividend by 100, and preponderating enantiomer by the concentration of the Enantiomeric enrichment of a mixture of enantiomers is calculated by dividing the concentration of the expressing the result as a percent. Enantiomeric preferably from about 10% to about 100%, and more enrichment can be from about 1% to about 100%, preferably from about 20% to 100%.

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compounds of the present invention, substituents R¹ and carbon can include ethyl, n-propyl, n-butyl, n-pentyl, lsobutyl, isopropyl, -CH;C(=0)C,H;, -CH,OC,H;, and -CH,O-R are identical, for example n-butyl/n-butyl, so that R¹ and R² can be selected from among substituted the compound is achiral at the 3-carbon. Bliminating (4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl containing heterocycles joined to the C, to C, alkyl through an ether linkage. Substituents at the 3-In certain particularly preferred alkylcarbonyl, alkoxy, hydroxy, and nitrogenand unsubstituted C, to C, alkyl wherein the substituent(s) can be selected from among are preferred.

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selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport Inhibitor

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optical isomerism at the 3-carbon simplifies the

carbonylalkyl amine, haloalkylthio, haloalkyleulfinyl, In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R*) the benzo- ring can include hydrogen, aryl, alkyl, ilkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxyhydroxy, halo, alkoxy, alkylthio, alkylsulfinyl, haloalkylsufonyl, amino, N-alkylamino, N,N-

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iryloxycarbamoyl, (N)-aralkyloxycarbamoyl, italkylamino, (N)-alkoxycarbamoyl, (N)-

example the 6,7,8-trimethoxy compounds. A variety of included are the 6,7,8-trialkoxy compounds, for disubstituted at the 7- and -8 positions. Also can be mono-substituted at the 6, 7 or 8 position, or pharmaceutically acceptable anion. The benzo ring is methylpyrrolidinium, and - (OCH2CH2),I, where A is a butyloxycarbamoyl, (N)-methylsulfonamido, (N)N'-- (N) -N'-dimethylpiperazinium I', (N)-t-N-hexylamino, thiophene, -N'(CH₃)₂CO₃H I', -NCH₃CO₃H, and N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)carboxyethylamino, (N)-morpholinyl, (N)-azetidinyl, -NHC(=0)CH₃, -NHC(=0)C₅H₁₁, -NHC(=0)C₅H₁₃, salt, and (N)-nitrogen containing heterocycle wherein w. is 2 or 3 and X is a halo or a quaternary ammonium (N)-N-methylazetidinium A, (N)-pyrrolidinyl, pyrrolyl, (N)-benzyloxycarbamoyl, trimethylammonium, A. dimethylamino, N,N-diethylamino, ethylthio, amino, hydroxylamine, N-methylamino, N,Niodo, bromo, fluoro, methylsulfinyl, methylsulfonyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, constitute R* are methyl, ethyl, isopropyl, t-butyl, quaternized. Among the preferred species which may the nitrogen of said heterocycle is optionally substituted thereon, $-[O(CH_3)_*]_*-X$ where x is 2 to 12. substituent on one or more of the alkyl substituents (N)-N-methylpyridinium A, (N)-N-methylmorpholinium A, benzyl ester, N-acylamine, hydroxylamine, trialkylammonium salt, (N)-carbamic acid, alkyl or sulfonamido, (N)-alkylsulfonamido, (N)trialkylammonium (especially with a halide an alkylene bridge having a quaternary ammonium salt ammonium salt having a carboxylic acid or hydroxy haloacylamine, carbohydrate, thiophene a trialkyl haloalkylsulfonamido, carboxyalkyl-amino -N, N-dialkylamido, (N)-haloalkylamido, (N)counterion), (N)-amido, (N)-alkylamido, -N-alkylamido

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N'R11R14R11A', where x is 2 to 10. carbohydrate (e.g., a 5 or 6 carbon monosaccharide), including, for example, guanidinyl, cycloalkyl, the 6, 7, 8, and/or 9- positions of the benzo ring, ring via poly(oxyalkylene) linkages, e.g., - $\{OCH_1CH_2\}_{g}$ peptide, and quaternary ammonium salts linked to the other substituents can be advantageously present on

30 20 25 15 10 of the aryl ring. Other substituents that can be substituted at the p-position, the m-position, or both tetra(oxyethylene)trimethyl-ammonium iodide, each hexylenetrimethylammonium, tri(oxyethylene)iodide, and formyl, acetyl, propanoyl, (N)-hexyldimethylammonium, chloride counterion), methoxycarbonyl, ethoxycarbonyl, trimethylammonium (preferably with an iodide or fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, substituted. Among the species which may constitute \mathbf{R}^{ullet} is preferably phenyl, phenylene, or benzene triyl, salt, thiophene, pyridine, pyrrole, thiazole, or 3 and X comprises halo or a quaternary ammonium dioxyalkylene, $-[O(CH_2)_v]_x$ where x is 2 to 12, w is 2 alkylcarbonyloxy and arylcarbonyloxy, (0,0)the substituents on the aryl ring of R' or R' are i.e., may be unsubstituted, mono-substituted, or disubstituted thereon, alkoxycarbonyl, aryloxycarbonyl, alkylene bridge having a quaternary ammonium salt N,N-dialkylamino, quaternary ammonium salts, a c_i to c_i and R' are independently selected from among hydrogen which the substituent(s) are selected from among halo, N-alkylpiperazinium, N-alkylmorpholinium, or furan in thiophene, pyridine, pyrrole, thiazole, imidazole, and ring-carbon substituted or unsubstituted aryl, imidazole, pyrazole, or furan. The aryl group of R' or hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, pyrazole, pyrimidine, morpholine, N-alkylpyridinium, In further compounds of the present invention, R1

present on a phenylene, benzene triyl or other

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1-phenyl, I m-(CH₁),-N'-CH₂CH₂-(OCH₂CH₃),-O-phenyl, I pproperties are those in which R or R is selected from ring) and 3,4-dioxyethylene (6- membered ring). Among dimethylaminophenyl, I p-(CH,),-N'-phenyl, I m-(CH,),fluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3ilmethylpiperazinium) - (N') - CH₂ - (OCH₂CH₂), -O-phenyl, 3dimethylpiperazinium) - (N') - CH2- (OCH2CH2)2-0-phenyl, 3aromatic ring include 3,4-dioxymethylene (5-membered compounds which have been or can be demonstrated to preferred R' substituents in combination with the R* have desirable ileal bile acid transport inhibiting nydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, msholorothienyl-2-yl, 3,4-difluorophenyl, I p-(N,Nsubstituents shown in Table 1. It is particularly Preferred compounds include 3-ethyl-3-butyl and 3dioxyethylenephenyl, and p-methoxycarbonylphenyl. outyl-3-butyl compounds having each of the above methoxyphenyl, p-N,N-dimethylaminophenyl, m-N,Npyridinyl, N-methyl-4-pyridinium, I' N-methyl-3preferred that one but not both of R's and R' is CH3),-N'-CH2CH2-(OCH2CH2),-O-phenyl, I m-(N,Ncyridinium, 3,4-dioxymethylenephenyl, 3,4phenyl, p-fluorophenyl, m-fluorophenyl, pmethoxy-4-fluorophenyl, thienyl-2-yl, 5hydrogen.

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It is especially preferred that R' and R' be hydrogen, that R' and R' not be hydrogen, and that R' and R' be oriented in the same direction relative to the plane of the molecule, i.e., both in α- or both in β-configuration. It is further preferred that, where R' is butyl and R' is ethyl, then R' has the same orientation relative to the plane of the molecule as R' and R'.

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Set forth in Table 1A are lists of illustrative species of $R^1/R^3\,,\;R^5/R^6$ and $R^\pi\,,\;$

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Table 1A: Alternative R Groups

$$(R^{X})_{q}$$
 $(R^{X})_{q}$
 $(R^{X})_{q}$

	, x,	e e	(R*)q
	ģ	Ph.	7-methy1
	#	p-P-Ph-	7-ethyl
		m-P-ph-	7-iso-propyl
		0.000	7-tert-bury
			-C
		p-cajo-ru-	
		m-CHJO-Pir-	1
		p-(CH ₁) ₂ N-Ph-	7-0(180-propyl)
		a- (CH,) N-Ph-	1-8CH3.
		10 11 11	7-80CH ₃
		7 . p-(CH3)3-N-Pn-	7-80,0%
۳.		I., a-(Qi,)1-N-Ph-	7-804-04
of the		I. p-(CH.)N-CH.CH	7. Mar.
		(OCH-CH-)O-Ph-	Torn-C
			7-1000
		י ווייין וריין ווייין ווייין ווייין	The state of
		(OCH2CH2) 2-0-Ph-	1-N(CH2) 2
		I', p-(N,N-	7-W (CH)), I
		dimethylphogratine) -	7-NHC(-0) CH,
		(N.) -CH (OCH.CH.)0-	7-N(CH-CH-)
		-40	1 (Carlotte)
			- Mrdungungu
		N'N) -B ' T	7-W*(Ma), CH, CO, H, I.
		dimethylpiperatine) -	7- (N) -morrohol ine
		(N.) -CH3 - (OCH3CH3) 3-0-	7. (N) -Aratidina
		-bh-	To (M) - Manage that a see that the
		m-P, p-CH ₁ 0-Ph-	- (m) -w-maching reservation,
		1. 4 dioxomerhylene.ph	
		B-CH.O. D-P-Dh-	7-(N)-pyrrolidine
			7-(N)-N-methyl-
			pyrrolidinium, I-
		N-methyl-4-pyridinium, I	7- (N) -N-methyl-
		3-pyridine	morpholinium, I-
		N-methyl-3-pyridinium, I'	7-(N)-N'-methylpiperagine
		2-pyridine	7- (N) -N -
		p-CH,0,C-Ph-	dimethylpiperasinium.
		thienvi-2-vi	
		5-C1-thienyl-2-vl	2-NH-CB2
			7-NHC(0) C-H
			1 - M-CO CONT C
			7-NH-C(NH)NH.
			7-(3)-thiophene

continued next page...

```
9-(N)-pyrrolidine
9-(N)-wanthyl.
9-(N)-Wanthyl.
9-(N)-Wanthyl.
9-(N)-Wanthyl.
9-(N)-Wanthylpiperasine
9-(N)-Wanthylpiperasinium,
1-mathylpiperasinium,
                                                                                                                                                                                                                                                                                                                                                                             9-N'(CM;);, I'
9-N'(CM;);,
9-N'(CH;CM;);
9-N'+CH;CM;
9-N'+CH;CO;H; I'
9-N'+CH;CO;H; I'
9-(N)-asetiding
9-(N)-asetiding
1'
1'
7-0CH<sub>3</sub>, 8-0CH<sub>3</sub>
7-8CH<sub>3</sub>, 8-0CH<sub>3</sub>
7-8CH<sub>3</sub>, 8-8CH<sub>3</sub>
6-0CH<sub>3</sub>, 7-0CH<sub>3</sub>, 8-0CH<sub>3</sub>
                                                                                              9-NH-CB2
9-NHC(0) C<sub>2</sub>H<sub>11</sub>
9-NHC(0) Cl<sub>3</sub>Br
9-NH-C(NI) NH<sub>2</sub>
9-(2) -thiophene
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       -O(iso-propy1)
```

8-N(CH₂CH₃)₂ 8-NHoCH₃CO₂H. 1 8-NHO₂CH₂CO₂H. 1 8-(N)-exetidine 9-(N)-setidine 9-(N)-setidine

B. (N) -pyrrolidine
G. (N) -k-methyl.

Flyrrolidinium, I.

Gly-N-methyl.

Borpholitium, I.

Gly-N'-methylpipersinium,
Gli-N'-methylpipersinium,
dimethylpipersinium, 8-NH-CBZ 8-NHC(0) C₅H₁₁ 8-NHC(0) CH₃Br 8-NH-C(NH) NH₃ 8-(2) -thiophene continued next page...

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8-0(iso-propyl) 8-SCH₃

Further preferred compounds of the present invention comprise a core structure having two or more pharmaceutically active benzothiepine structures as described above, covalently bonded to the core molety via functional linkages. Such active benzothiepine structures preferably comprise:

(Formula DIV)

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or:

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(Formula DIVA)

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where R¹, R², R¹, R⁴, R⁴, R⁴, R¹, R¹, K, ¼, q and n are as defined above, and R⁴ is either a covalent bond or arylene.

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The core moiety can comprise alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkyne diyl, polyalkane diyl, alkoxy

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diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by 0, NR', N'R'R', S, SO, SO2, S'R'R', PR7, P+R7R8, phenylene, heterocycle, quaternary heterocycle, quaternary heterocycle,

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, SO₃R⁷, CO₂R⁷, CN, OXO, CONR⁷R⁸, N⁴R⁷R⁸R⁸A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, p(O)R⁷R⁸, p⁴R⁷R⁸A-, and P(O)(OR⁷OR*, and

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N⁺R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, PR⁷, PR⁷, PR⁷, PR⁷, PR⁷, PR⁷, Or phenylene.

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Exemplary core moleties include:

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wherein:

 R^{13} is selected from the group consisting of C and

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N, and

 R^{24} and R^{27} are independently selected from the group consisting of:

H

H

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wherein R¹⁸, R¹⁹ and R¹¹ are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

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A'is a pharmaceutically acceptable anion, and k=1 to 10.

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In compounds of Formula DIV, R³⁰, R³¹, R²¹ in Formula DIII can be bonded at any of their 6-, 7-, 8-, or 9- positions to R¹⁹. In compounds of Formula DIVA, it is preferred that R¹⁵ comprises a phenylene molety bonded at a m- or p-position thereof to R¹⁹.

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In another embodiment, a core moiety backbone, R¹⁹, as discussed herein in Formulas DII and DIII can be multiply substituted with more than four pendant active benzothiepine units, i.e., R²⁰, R²¹, R²¹, and R²¹ as discussed above, through multiple functional groups

within any of the groups encompassed by the definition ictive benzothiepine units within a single core moiety about one to about 100, preferably about one to about points of attachment of similar or different pendant backbone unit, R19, can comprise a single core moiety individual core moiety backbone units can range from nore preferably about one to about 25. The number of unit, multimers thereof, and multimeric mixtures of 30, more preferably about one to about 50, and even backbone unit can be in the range from about one to Such points of the different core moiety units discussed herein, about 100, preferably about one to about 80, more ittachment can include bonds to C, S, O, N, or P within the core moiety backbone. The core moiety preferably about one to about 50, and even more l.e., alone or in combination. The number of preferably about one to about 25. of R.

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The more preferred benzothiepine moieties comprising R²⁰, R²¹, R²¹ and/or R²¹ conform to the preferred structures as outlined above for Formula I. The 3-carbon on each benzothiepine moiety can be achiral, and the substituents R¹, R², R³, R⁴, R⁴ and R² can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(exyalkylene) or oligo(oxyalkylene), especially oly- or oligo(exyethylene) or poly- or

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Dosages, Formulations, and Routes of Administration

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The ileal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of

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action in the body, for example in the ileum of a mammal, e.g., a human.

For the prophylaxis or treatment of the conditions referred to above, the compounds of the present invention can be used as the compound per se.

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particularly suitable for medical applications because pharmaceutically acceptable acid addition salts of the particularly preferred for medical purposes. Suitable pharmaceutically acceptable anion or cation. Suitable nydrochloric, hydrobromic, phosphoric, metaphosphoric, methanesulfonic, succinic, toluenesulfonic, tartaric, ummonium salts, alkali metal salts such as sodium and citric, ethanesulfonic, fumaric, gluconic, glycolic, nclude those derived from inorganic acids, such as of their greater aqueous solubility relative to the utric, sulfonic, and sulfuric acids, and organic potassium salts, and alkaline earth salts such as parent compound. Such salts must clearly have a compounds of the present invention when possible and trifluoroacetic acids. The chloride salt is lsothionic, lactic, lactobionic, maleic, malic, cids such as acetic, benzenesulfonic, benzoic, pharmaceutically acceptable base salts include Pharmaceutically acceptable salts are

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The anions of the definition of A in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

magnesium and calcium salts.

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The compounds of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably

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with pharmaceuticals, either as individual therapeutic compounds. compounds or as a combination of therapeutic conventional means available for use in conjunction These compounds can be administered by any

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compound chosen, the use for which it is intended, the depend on a number of factors such as the specific the recipient. mode of administration, and the clinical condition of achieve the desired biological effect will, of course, The amount of compound which is required to

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sustained release form effective to obtain desired administered 2 to 6 times per day. Doses can be in proportionate multiple subdoses. Subdoses can be administered to the patient in a single dose, or in 10 mg/kg bodyweight/day. This total daily dose can be bodyweight/day, more preferably from about 3 to about preferably from about 1 mg to about 50 mg/kg from about 0.3 to about 100 mg/kg bodyweight/day. In general, a daily dose can be in the range of

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In the case of pharmaceutically acceptable salts, the preferably from about 10 to about 50 mg of compound. preferably about 1 to about 75 mg of compound, more about 0.1 to about 100 mg of benzothiepine compound, as tablets or capsules, can contain, for example, from Orally administrable unit dose formulations, such

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weights indicated above refer to the weight of the

benzothiepine ion derived from the salt. Oral delivery of an ileal bile acid transport

acid methyl ester. anionic polymers of methacrylic acid and methacrylic phthalate, hydroxypropylmethylcellulose phthalate and cellulose acetate phthalate, polyvinylacetate invention. Suitable enteric coatings include formulations are within the scope of the present enteric-coated and enteric-coated controlled release molecule is delivered to the site of action (the extend the time period over which the active drug drug from the dosage form. The intended effect is to of the small intestine, slow erosion of a tablet or ileum) by manipulation of the dosage form. Thus, the dosage form to the mucosal lining of the physical properties of the formulation, bioadhesion of release from the dosage form based on the changing pH prolonged or sustained delivery of the drug to the intestinal tract, or enzymatic release of the active capsule, retention in the stomach based on the These include, but are not limited to, pH sensitive gastrointestinal tract by any number of mechanisms formulations, as are well known in the art, to provide inhibitor of the present invention can include

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purpose can contain, for example, from about 0.1 ng to body weight, more preferably from about 0.4 mg/kg body about 10 mg, preferably from about 1 ng to about 10 mg weight per minute. Infusion fluids suitable for this about 10 ng/kg body weight to about 100 ng/kg body be conveniently administered as an infusion of from weight to about 0.6 mg/kg body weight. This dose can from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight to about 1.0 mg/kg body weight, preferably for example, be in the range of from about 0.1 mg/kg When administered intravenously, the dose can,

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Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

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one or more assessory ingredients. Compressed tablets granules optionally mixed with a binder, lubricant, or non-aqueous liquid; or as an oil-in-water or watercan be prepared by compressing, in a suitable machine, then, if necessary, shaping the product. For example, the compound in a free-flowing form, such as a powder .n-oil emulsion. As indicated, such compositions can such as capsules, cachets, lozenges, or tablets, each granules; as a solution or a suspension in an aqueous be prepared by any suitable method of pharmacy which iquid or finely divided solid carrier, or both, and a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with general, the compositions are prepared by uniformly ind intimately admixing the active compound with a ncludes the step of bringing into association the constitute one or more accessory ingredients). In Pharmaceutical compositions suitable for oral idministration can be presented in discrete units, containing a predetermined amount of at least one compound of the present invention; as a powder or active compound(s) and the carrier (which can

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inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

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Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

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Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

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Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active

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compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Pharmaceutical compositions suitable for transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in pharmaceutical Research, 3(6), 318 (1986).

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In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

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The solid dosage forms for oral administration including capsules, tablets, pills, powders, and granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

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Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions,

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solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

acid find use in the preparation of injectables. oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic suspending medium. For this purpose any bland fixed oils are conventionally employed as a solvent or sodium chloride solution. In addition, sterile, fixed the acceptable vehicles and solvents that may be dispersing or setting agents and suspending agents. employed are water, Ringer's solution, and isotonic sterile injectable solution or suspension in a The sterile injectable preparation may also be a for example, as a solution in 1,3-butanediol. Among nontoxic parenterally acceptable diluent or solvent, formulated according to the known art using suitable injectable aqueous or oleaginous suspensions may be Injectable preparations, for example, sterile

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Pharmaceutically acceptable carriers encompass all the foregoing and the like.

Treatment Regimen

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The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological

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evels by any of the methods well known in the art, to monitored by, for example, measuring serum cholesterol so that the duration of treatment can be determined as schedule can be rationally modified over the course of continued as necessary over a period of several weeks Initial treatment of a patient suffering from a herapy so that the lowest amount of ileal bile acid nvention are administered at any point in time, and and so that administration is continued only so long disease condition has been controlled or eliminated. whibits satisfactory effectiveness is administered, hyperlipidemic condition can begin with the dosages to several months or years until the hyperlipidemic Patients undergoing treatment with the compounds or determine the effectiveness of therapy. Continuous transport inhibitor of the present invention which analysis of such data permits modification of the well. In this way, the treatment regimen/dosing reatment regimen during therapy so that optimal indicated above. Treatment should generally be compositions disclosed herein can be routinely iffective amounts of compounds of the present as is necessary to successfully treat the nyperlipidemic condition.

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illustrate various aspects of the present invention. The following non-limiting examples serve to

EXAMPLES OF SYNTHETIC PROCEDURES

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Preparation 1

2-Ethyl-2-(mesyloxymethyl)hexanal (1)

chloride extract was dried over MgSO, and concentrated procedure described in Chem. Ber. 98, 728-734 (1965), triethylamine was added dropwise 15.8 g of 2-ethyl-2while maintaining the reaction temperature below 30 To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of temperature for 18 h, quenched with dilute HCl and (hydroxymethyl)hexanal, prepared according to the extracted with methlyene chloride. The methylene C. The reaction mixture was stirred at room In vacuo to give 24.4 g of brown oil.

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Preparation 2

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2-((2-Benzoylphenylthio)methyl)-2-ethylhexenal (2)

A mixture of 31 g (0.144 mol) of 2-

of 2-ethyl-2-(mesyloxymethyl)-hexanal (1), 14.8 g procedure described in WO 93/16055, 24.4 g (0.1 mole) mercaptobenzophenone, prepared according to the

methoxyethyl ether. The residue was purified by HPLC dried over MgSO, and concentrated in vacuo to remove 2chloride layer was washed with 300 mL of 10% NaOH, with 300 mL of methylene chloride. The methylene methoxyethyl ether was held at reflux for 24 h. The (10% EtOAc-hexane) to give 20.5 g (58%) of 2 as an reaction mixture was poured into 3N HCl and extracted (0.146 mole) of triethylamine, and 80 mL of 2-

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Scheme 6

sulfide to sulfone yielded the key intermediate w. alcohol to benzyl bromide, followed by oxidation of by the addition of dialkyl mesylate aldehyde (\mathbf{x}) , polar solvent (such as DMF, DMA, DMSO, etc.), followed appropriately substituted 2-fluorobenzaldehyde with Generic Scheme X: The nucleophilic substitution of an benzyl alcohol monoaldehyde Z. Conversion of benzyl reduction of the dialdehyde at low temperature yielded provided a dialkyl benzene dialdehyde Y. DIBAL lithium sulfide or other nucleophilic sulfide anion in

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the cyclic sulfate as the reagent. reagent as shown in the following schemes XI and XII. synthesized using cyclic sulfate (XL, below) as the The following examples describe a procedure for using The compounds of this invention can also be

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3. H2SQ4

benzothiepine-1,1-dioxides, particularly 3,3-dialkyl Scheme XI illustrates yet another route to

analogs, starting from the thiophenol XVIIIA.
Thiophenol XVIIIA can be reacted with cyclic sulfate
XL to give the alcohol XLI which can be oxidized to
yield the aldehyde XLII. Aldehyde XLII itself can be
further oxidized to give the sulfone XLIII which can
be cyclized to give a stereolsomeric mixture of
benzothiepine XLIVa and XLIVb.

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Thiophenol XVIIIA can be prepared according to Scheme 3 as previously discussed and has the following formula:

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XVIIIA

wherein R*, R* and q are as previously defined for the compounds of formula I. Cyclic sulfate XL can be prepared according to synthetic procedures known in the art and has the following formula:

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wherein R¹ and R² are as previously defined for the compounds of formula I. Preferably, R¹ and R² are alkyl; more preferably, they are selected from the group constating of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl, and still more preferably, R¹ and R² are n-butyl.

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In the process of Scheme XI, thiophenol XVIIIA is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as methoxyethyl ether. While the reaction

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conditions such as temperature and time are not narrowly critical, the reaction preferably is allowed to proceed at about room temperature for about two hours. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield can be improved by using about 1.01 to 1.3 equivalents of cyclic sulfate XL for each equivalent of thiophemol XVIIIA present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of thiophemol XVIIIA present.

In the process of the invention, thiophenol XVIIA also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing thiophenol XVIIIA prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the hydrogen atom from the mercaptan group attached to the benzene ring of thiophenol XVIIIA. The resulting sulfur anion of the thiophenol then reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the thiophenol then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate

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The abstracting agent generally is a base having a pH greater than about 10. Preferably, the base is an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; more preferably, the base is sodium hydride. A slight excess of abstracting agent is preferred relative to thiophenol XVIIIA. Reaction time and yield is improved by using about 1.0 to about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA

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present. More preferably, this ratio is about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA present.

The sulfate group of the intermediate product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield alcohol XLI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid.

The several reactions involving thiophenol XVIIIA, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need for isolation of any of the intermediates produced.

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Alcohol XII is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to aldehyde XIII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

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Aldehyde XIII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde XIII. Preferably, the oxidizing agent is metachloroperbenzoic acid.

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Sulfone-aldehyde XLIII likewise is isolated by conventional methods and then cyclized to form the stereoisomeric benzothiepines XLIVa and XLIVb. The cyclizing agent preferably is a base having a pH between about 8 and about 9. More preferably, the base is an alkoxide base, and still more preferably, the base is potassium tert-butoxide.

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The two oxidation steps of Schems XI can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield

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a sulfone-alcohol which is then oxidized to yield a sulfone-aldehyde.

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Scheme XII 113

analogs, starting from the halobenzene L. Halobenzene sterecisomeric mixture of benzothiepine LIVa and LIVb. above to give the alcohol LI which can be oxidized to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl yield the sulfone-alcohol LII, Sulfone-alcohol LII itself can be further oxidized to give the sulfone-Scheme XII illustrates still another route to L can be reacted with cyclic sulfate XL disclosed aldehyde LIII which can be cyclized to give a

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Halobenzene L (which is commercially available or halobenzenes by one skilled in the art) has the can be synthesized from commercially available following formula:

wherein R3, Rx, and q are as previously defined for the

compounds of formula I; R^b is a halogen such as chloro,

withdrawing group at the ortho or para position of the group. Cyclic sulfate XL can be prepared as set forth halobenzene, and is preferably a p-nitro or o-nitro in Scheme XI and can have the following formula: promo, fluoro or iodo; and R° is an electron

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n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; group consisting of methyl, ethyl, propyl, isopropyl, wherein R¹ and R² are as previously defined for the alkyl; more preferably, they are selected from the compounds of formula I. Preferably, R' and R' are and still more preferably, R' and R' are n-butyl

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reaction preferably is conducted in an aprotic solvent and more preferably, in dimethyl formamide. Although the reaction conditions such as temperature and time such as dimethyl formamide or N:N-dimethylacetamide, In the process of Scheme XII, halobenzene L is initially reacted with cyclic sulfate XL. This

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for about 8 to 12 hours. More preferably, the are not narrowly critical, the reaction preferably is allowed to proceed at between about 70°C and about 90°C

XL for each equivalent of halobenzene L present. this ratio is about 1.1 equivalents of cyclic sulfate equivalent of halobenzene L present. More preferably, to 1.3 equivalents of cyclic sulfate XL for each Reaction time and yield is improved by using about 1.1 stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred reaction preferably employs an approximately reaction temperature is maintained at about 80°C. The

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sulfur anion reacts with cyclic sulfate XL to open the the benzene ring of halobenzene L and replaces that then bonds with a terminal carbon atom of the open sulfate ring. The sulfur anion of the halobenzene atom with a divalent sulfur atom. The resulting abstracting agent removes the halogen atom attached to being held to a particular theory, it is believed the or after the addition of cyclic sulfate XL. Without containing halobenzene L prior to, concurrently with, abstracting agent can be added to the solvent also is treated with an abstracting agent. The In the process of the invention, halobenzene L

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of halobenzene L present. relative to halobenzene L. Reaction time and yield is sulfide, and preferably it is dilithium sulfide. A of the open ring sulfate is the sulfate group. ring sulfate. The terminal group at the unbonded end equivalents of abstracting agent for each equivalent present. More preferably, this ratio is about 1.05 abstracting agent for each equivalent of halobenzene L improved by using about 1.01 to 1.3 equivalents of slight excess of the abstracting agent is preferred abstracting agent generally is a dialkali metal

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The sulfate group of the product of the reaction

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alkali metal hydroxide, preferably sodium hydroxide of an ester and alcohol LI. Suitable hydrolyzing removed, preferably by hydrolysis, to yield a mixture of thiophenol XVIIIA with cyclic sulfate XL is then then converted to alcohol LI by treatment with an hydrochloric acid and sulfuric acid. The ester is agents include mineral acids, particularly

need to isolate any of the intermediates produced. hydrolyzing agent can take place in situ without the salicylate) and oxidized using standard oxidizing methods (for example, extraction with aqueous methyl cyclic sulfate XL, the abstracting agent and the Alcohol LI is then isolated by conventional The several reactions involving halobenzene L,

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such as methylene chloride or chloroform. reaction is conducted in a suitable organic solvent oxidizing agent is metachloroperbenzoic acid. The Sulfone-alcohol LII is then isolated by

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agents to sulfone-alcohol LII. Preferably, the

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chloride or chloroform. pyridinium chlorochromate, and more preferably, it is Preferably, the oxidizing agent is sulfur trioxide or standard oxidizing agents to sulfone-aldehyde LIII. in a suitable organic solvent such as methylene pyridinium chlorochromate. The reaction is conducted conventional methods and further oxidized using

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procedure previously set forth in Scheme XI. desired benzothiepine-1,1-dioxides according to the Sulfone-aldehyde XLIII is then converted to the

can be oxidized first to yield an aldehyde which is then oxidized to yield a sulfone-aldehyde. adversely affecting the overall reaction. The two oxidation steps can be reversed without Alcohol XLI

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overall yield and avoids many of the purification mesylate reagent in Schemes XI and XII improves the Use of the cyclic sulfate reagent instead of a

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difficulties encountered relative to those reaction schemes proceeding through a mesylate intermediate. Overall yields are significantly improved when a cyclic sulfate is used instead of a mesylate reagent. In addition, chromatographic separation of the intermediate product of the cyclic sulfate coupling step of the reaction is not necessary. For example, in Schemes XI and XII the intermediate is a water soluble alkali metal salt and the impurities can be removed by extraction with ether. The intermediate is then hydrolyzed to the desired alcohol.

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Example Corresponding to Scheme XI:

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Step 1: Preparation of 2,2-dibutyl-1,3-propanediol:

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Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyldiethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated under vacuum to give 98.4 g (yield 95%)

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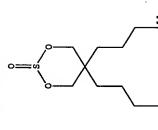
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of the diol as an oil. Proton NMR, carbon NMR and MS confirmed the product.

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Step 2: Dibutyl-cyclic-sulfite:



A solution of the dibutyl-diol of step 1 (103 g, 0.5478 mol) in anhydrous methylene chloride (500 ml) and triethylamine (221 g, 4 equivalents, 2.19 mol) was stirred at 0°C under nitrogen. Thionyl chloride (97.78 g, 0.82 mol) was added dropwise to the mixture. Within 5 minutes the solution turned to yellow and then to black when the addition was completed within about half an hour. The reaction was completed within 3 hours (gas chromatography confirmed no starting material was left). The mixture was washed with ice water twice, and brine twice. The organic phase was dried over magnesium sulphate and concentrated under vacuum to give 128 g (yield 100%) of the dibutyl-cyclic-sulfite as a black oil. NMR and MS were consistent with the product.

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Step 3: Dibutyl-cyclic sulfate:

To a solution of the dibutyl-cyclic-sulfite of step 2 (127.5 g, 0.54 mol) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium(III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. Gas chromatography confirmed there was no starting material left. The mixture was extracted once with 300 ml of ether and three times with brine. The organic phase was dried over magnesium sulphate and passed through celite. The filtrate was concentrated under vacuum and gave 133 g (yield 97.8%) of the dibutyl-cyclic-sulfate as an oil. Proton NMR, carbon NMR and MS confirmed the product.

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<u>Step 4</u>: 2-[(2-4'-fluorobenzyl-4-methylphenylthio)
methyl]-2-butylhexanol:

Proton NMR, C13-NMR and MS confirmed the product. give 2.47 g (yield 92.5%) of the hexanol as an oil. and boiled for 10 minutes. The mixture was cooled and ml of 10% NaOH was added. This aqueous mixture was ether two times. The water layer was separated and 20 mmole) in 10 ml of methoxyethyl ether was then added. mixture of diphenylmethane thiophenol (1.55 g, 6.68 6.68 mmole) was washed with hexane. The hexane was magnesium sulphate, and concentrated under vacuum to successively with water and brine, dried over extracted with ether. The organic layer was washed boiled for 30 minutes, cooled, acidified with 6N HCI, Gas chromatography confirmed there was no thiol left. 0°C and 1 hour at room temperature under nitrogen. the dibutyl-cyclic-sulfate of step 3 (2.17 g, 8.66 dropwise over a period of 15 minutes. A mixture of decanted and 20 ml of methoxyethyl ether was added to mmole) in 10 ml of methoxyethyl ether was added the washed sodium hydride and cooled in an ice bath. A The resulting mixture was stirred for 30 minutes at The solvent was evaporated and washed with water and A 60% oil dispersion of sodium hydride (0.27 g,

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methylphenylthio)methyl]-2-butylhexanal: Step 5: 2-[(2-4'-fluorobenzyl-4-

vacuum to give 1.39 g (yield 70%) of the hexanal as an mmole) in 40 ml of methylene chloride cooled in an ice To a solution of the hexanol of step 4 (2 g, 4.9 mixture was stirred for 3 hours and filtered through chlorochromate (2.18 g, 9.9 mmole). The reaction oil. Proton NMR, carbon NMR and MS confirmed the silica gel. The filtrate was concentrated under bath under nitrogen was added pyridinium product.

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Step 6: 2-[(2-4'-fluorobenzyl-4-methylphenylsulfonyl) methyl]-2-butylhexanal

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1.1 mmole) in 20 ml of methylene chloride cooled by an To a solution of the hexanal of step 5 (0.44 g, The metachloroperbenzoic acid (0.54 g, 2.2 mmole). reaction mixture was stirred for 18 hours and ice bath under nitrogen was added 70 %

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sulphate, and concentrated under vacuum to give 0.42 g 10% NaOH(3X), water, and brine, dried over magnesium filtered. The filtrate was washed successively with (yield 90%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

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phenyl) -2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide: Step 7: Cis-3,3-dibutyl-7-methyl-5-(4'-fluoro-

raction came as 0.1 g of the starting material in the mmole) in 30 ml of anhydrous THF was stirred in an ice butoxide (102 mg, 0.85 mmole) was then added. After 3 hours thin layer chromatography confirmed the presence A mixture of the hexanal of step 6 (0.37 g, 0.85 bath at a temperature of about 0° C. Potassium-tertand concentrated under vacuum. This concentrate was form of an oil. The second fraction yielded 0.27 g (75% yield) of the desired benzothiepine as a white successively with water and brine, dried with MgSO,, solid. Proton NMR, carbon NMR and MS confirmed the material. The crude reaction mixture was acidified of the product and a small amount of the starting purified by HPLC (10% BtOAc-Hexane). The first with 10% HCl, extracted with ether, washed product. (M+H=433).

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Example Corresponding to Scheme XII

Step 1: 2-[(2-4'-methoxybenzyl-4-nitrophenylthio)methyl]-2-butylhexanol:

overnight. The solution was cooled to 0°C and equivalents) was added. The solution color changed to ml of DMF and lithium sulfide [1.75 g, 1.05 chloride, filtered through silica gel, eluted with 20% over magnesium sulphate, and concentrated under was washed successively with water and brine, dried and extracted with ethyl acetate. The organic layer with 3M of NaOH for 1 hour. The mixture was cooled and brine, dried over magnesium sulphate, and mixture was cooled and extracted with ethyl acetate. added and the reaction mixture boiled overnight. The water and ether (three times). The water layer was solvent was evaporated and washed successively with added and stirred at room temperature overnight. The Step 3 of the Scheme XI examples) in 10 ml of DMF was dibutyl-cyclic-sulfate (9.9g; prepared as set forth in red. The reaction mixture was heated at 80°C ethyl acetate and hexane, and concentrated under concentrated under vacuum. The product was boiled The organic layer was washed successively with water separated and 40 ml of concentrated sulfuric acid was Chlorodiphenylmethane (10g) was dissolved in 25 The concentrate was dissolved in methylene

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vacuum to give 11.9 g (yield 74%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

5 Step 2: 2-[2-4'-methoxybenzyl-4-nitrophenylthio)methyl]-2-butylhexanal:

To a solution of the hexanol of step 1 (6 g, 13 mmole) in 50 ml methylene chloride cooled in ice bath under nitrogen was added 70% MCPBA (8.261 g, 33 mmole). The reaction was stirred for 18 hours at room temperature and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under vacuum to give 5 g (yield 77.7%) of the hexanal as a white solid, MP 58-60°C. Proton NMR, Cl3-NMR and MS confirmed the product.

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Example 1398

Step 1. Preparation of 2

organic layer was dried over MgSO, and concentrated in Waters Prep-2000) using ethyl acetate/hexanes (25/75) tetrakis (triphenylphosphine) palladium(0) (0.7 mmol) 2H), 3.20 (8, 2H), 4.59 (8, 2H), 6.93 (dd, J = 10.5 and 2.4 Hz, 1H), 7.15 (dt, J = 8.4 and 2.85 Hz, 1H), 0.99-1.38 (m, 8H), 1.62-1.75 (m, 2H), 1.85-2.00 (m, 7.46-7.59 (m, 2H), 8.05-8.16 (m, 3H), 9.40 (8, 1H). This heterogeneous mixture was refluxed for three hours, then cooled to ambient temperature and and 45 mL of a 2 M solution of sodium carbonate in gave 4.8 g (73%) of the title compound as a yellow 1 H NMR (CDCl₃) d 0.88 (t, J = 7.45 Hz, 6H), dialdehyde of Example 1395 (14.3 mmol) in 72 mL of Purification by silica gel chromatography partitioned between ethyl acetate and water. The To a solution of 6.0 g of dibutyl 4-fluorobenzene toluene and 54 mL of ethanol was added 4.7 g 3nitrobenzeneboronic acid (28.6 mmol), 0.8 g of racuo. solid. vater.

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Step 3. Preparation of 3

cooled to 0 °C in an ice bath. 20 mL of a 1 M solution MS(PABH+) m/e (relative intensity) 464.5 (100), 446.6 A solution of 4.8 g (10.4 mmol) of 2 in 500 mL THF was 30 minutes, then the reaction was guenched with 100 mL organic layer was washed with brine, then dried (MgSO,) and concentrated in vacuo. Purification by silica gel eluent yielded 4.3 g (90%) of 3 as a pale yellow foam. 6.0 Hz, 1H), 5.67 (B, 1H), 6.34 (dd, J=9.6 and 3.0 Hz, of potassium t-butoxide was added slowly, maintaining 3.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). the temperature at <5 °C. Stirring was continued for "H NMR (CDCl3) d 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 (qhB, JhB = 15.0 Hz, AV = 33.2 Hz, 2H), 4.17 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J = chromatography through a 100 ml plug using CH,Cl, as (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 partitioned between ethyl acetate and water; the of saturated ammonium chloride. The mixture was (65). HRMS calculated for M+H 464.1907. Pound

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464.1905.

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Step 4. Preparation of 4 127

471.5 (25). HRMS calculated for M+H 489.2423. Found Hz, 1H), 8.20 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (8, 6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4 = 9.0 Hz, 1H), 5.65 (8, 1H), 5.75 (d, J = 2.1 Hz, 1H), 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), NMR (CDC1₃) d 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), an ethyl acetate/hexanes gradient (10-40% ethyl vessel was sealed and heated to 110 °C for 16 hours. 1H). MS(FABH⁺) m/e (relative intensity) 489.6 (100); Hz, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.03.09 (qAB, JAB = 15.0 Hz, DV= 45.6 Hz, 2H), 4.90 (d, J acetate) gave 4.0 g (88%) of 4 as a yellow solid. H by silica gel chromatography (Waters Prep-2000) using and the contents concentrated in vacuo. Purification The reaction vessel was cooled to ambient temperature vessel was added 8.2 g dimethyl amine (182 mmol). The in 30 ml THF contained in a stainless steel reaction To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of

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Step 5. Preparation of 5 128

8.9 Hz, 1H). MS(FABH+) m/e (relative intensity) 459.7 J = 7.8 and 1.8 Hz, 1H), 6.83 (8, 1H), 6.93 (d, J =6H), 3.07 (qAB, JAB = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (e, of 5. H NMR (CDCl₃) d 0.80-0.98 (m, 6H), 1.00-1.52 (m, contents filtered to remove the catalyst. The psi) and heated to 45 °C for six hours. The reaction g 10% palladium on carbon. The reaction vessel was ethanol in a stainless steel Parr reactor was added 1 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = filtrate was concentrated in vacuo to give 0.9 g (96%) vessel was cooled to ambient temperature and the sealed, purged twice with H, then charged with H, (100 To a suspension of 1.0 g (2.1 mmol) of 4 in 100 ml (100). HRMS calculated for M+H 459.2681. Found Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, (8, 2H), 4.14 (8, 1H), 5.43 (8, 1H), 6.09 (d, J = 2.4

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Step 6. Preparation of 6

Next was added 4 g (39.6 mmol) TEA. The reaction was using a gradient of ethyl acetate (20-50%) in hexane as 6.9 Hz, 2H), 4.10 (8, 1H), 5.51 (8, 1H), 5.95 (d, J = silica gel chromatography through a 70 ml MPLC column 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 (qAB, JAB = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride. eluent yielded 0.9 g (73%) of 6 as a pale yellow oil. 2.4 Hz, 1H), 6.51 (dd, J = 9.3 and 2.7 Hz, 1H), 7.28 (8, 1H), 7.32-7.41 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), To a solution of 914 mg (2.0 mmol) of 5 in 50 ml THF (MgSO,) and concentrated in vacuo. Purification by stirred 10 minutes, then partitioned between ethyl ⁴H NMR (CDC1,) d 0.84-0.95 (m, 6H), 1.02-1.53 (m, ncetate and brine. The organic layer was dried 7.90 (d, J = 9.0 Hz, 1H).

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Step 7. Preparation of 7

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To a solution of 0.9 g (1.45 mmol) of 6 in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Purification by reverse-phase silica gel

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chromatography (Waters Delta Prep 3000) using an acetonitrile /water gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of 7 as a white foam. ¹H NWR (CDCl.) d 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (qAB, JAB = 15.6 Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J = 1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed 642.4343.

Example 1398a

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Step 1

C,4H,0ClNO, fw=291.69

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In an inert atmosphere, weigh out 68.3 gms phosphorus pentachloride (0.328mcle Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Fit flask with a N, inlet adapter and suba seal. Remove from inert atmosphere and begin N, purge. Add 50mls anhydrous chlorobenzene (Aldrich 28,451-3) to the PCl, via syringe and begin stirring with magnetic stir bar.

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Weigh out 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3). Slowly add to the chlorobenzene solution while under N, purge. Stir at

wt=61.95gms. Store in inert and dry atmosphere. Wash residue with anhydrous hexane. Dry acid chloride 50C for 1hr. Remove chlorobenzene by high vacuum. temperature for ~20hrs, place in oil bath and heat at room temperature overnight. After stirring at room

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5). Place solution in a 2-necked 500ml round bottom 105mls anhydrous anisole (0.97 mole Aldrich 29,629-In inert atmosphere, dissolve acid chloride with

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Slowly add AlCl, to chilled solution. After addition overnight . is complete, allow to warm to room temperature. Stir reaction solution with ice bath and begin N2 purge. N, inlet adapter. Remove from inert atmosphere. Chill funnel. Fit reaction flask with addition funnel and a Aldrich 29,471-3) and place in a solid addition Weigh out 45.1gms aluminum chloride (0.34 moles

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mls IN HCl and ice. Stir 15 min. Extract twice with Yield 41%. Obtain NMR and mass spec (m/z=292). by high vacuum. Crystalize product from 90% ethanol MgSO,, filter and rotovap to dryness. Remove anisole 2% NaOH, then twice with deionized H,O. Dry with ether. Combine organic layers and extract twice with 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms. Quench reaction by pouring into a solution of 300

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Step 2

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C14H12C1NO, fw=277.71

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Dissolve 38.10gms (0.131 moles) of the

inlet, addition funnel and stopper. Stir with magnetic chloride. Place in a 3 liter flask fitted with N₃ benzophenone from step 1 in 250mls anhydrous methylene stir bar. Chill solution with ice bath.

Stir 5 minutes after addition is complete. mls anhydrous methylene chloride. Place in addition sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 funnel and add dropwise to chilled solution under N, Prepare a solution of 39.32 gms trifluoromethane

after addition is complete. dropwise to chilled solution under N_2 . Stir 5 minutes methylene chloride. Place in addition funnel and add (0.197mole Aldrich 23,019-7) and 170mls anhydrous Prepare a solution of 22.85 gms triethyl silane

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after addition is complete. dropwise to chilled solution under N₁. Stir 5 minutes methylene chloride. Place in addition funnel and add trifluoromethane sulfonic acid and 170mls anhydrous Prepare a second solution of 39.32 gms

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under N, overnight. to slowly warm to room temperature overnight. Stir solution under N2. After all additions are made allow silane and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled Prepare a second solution of 22.85 gms triethyl

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methylene chloride. Dry organic layers with MgSO4. wt=28.8gms. Confirm by NMR and mass spec (m/z=278) Crystallize from ethanol. Dry on vacuum line. Dry organic layer and extract aqueous layer 2 times with separatory funnel and allow separation. Remove chilled temperature for 30 min. Pour into a vigorously, slowly add reaction mixture. Stir at beaker. Chill with ice bath. While stirring Prepare 1300 mls saturated NaHCO, in a 4 liter

Step 3

C15H11NO.S fw=443.61

Dissolve 10.12 gms (0.036 moles) of product 2 with 200 mls anhydrous DMSO. Place in a 500 ml round bottom flask with magnetic stir bar. Fit flask with water condenser, N, inlet, and stopper. Add 1.84 gms Li_{1,5}S (0.040 moles Aldrich 21,324-1). Place flask in oil bath and heat at 75°C under N, overnight then cool to room temperature.

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Weigh out 10.59 gms dibutyl mesylate (0.040 moles). Dissolve with anhydrous DMSO and add to reaction solution. Purge well with N_z , heat overnight at $80^{\circ}\mathrm{C}$.

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Cool to room temperature. Prepare 500 mls of 5% acetic acid in a 2 liter beaker. While stirring, slowly add reaction mixture. Stir 30 min. Extract with ether 3 times. Combine organic layers and extract with water and sat'd NaCl. Dry organic layer with MgSO,, filter and rotovap to dryness. Dry oil on vacuum line. Obtain pure product by column chromatography using 95% hexane and 5% ethyl acetate as the mobile phase. Dry wt=7.8 gms. Obtain NMR and mass spec (m/z=444).

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Step 4

C18H13NO6S fw-475.61

iry with MgSO,. Filter and rotovap to dryness. Obtain 8 hrs to convert to the sulphone. Chill solution over Dissolve 9.33 gms (0.021 moles) of product 3 with night in freezer. Filter solid from reaction, extract 120 mls anhydrous methylene chloride. Place in a 250 joes quickly to the sulphoxide intermediate but takes flask with N, inlet and stopper. Chill solution with filtrate with 10% K,CO,. Extract aqueous layer twice isolating by column chromatography. Obtain NMR and Combine organic layers and ml round bottom flask with magnetic stir bar. Fit semperature and monitor reaction by TLC. Reaction chloroperbenzoic acid (0.0435 moles, Fluka 25800, ce bath under N, purge. Slowly add 11.54 gms 3--65%). After addition is complete warm to room pure product by crystallizing from ethanol or with methylene choride. mass spec (m/z=476).

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Step 5

stir rate of 250 rpm. Run overnight under these under H₂. Run reaction at 200 paig H₂, 55°C, and a 20,569-9). Seal reactor before removing from glove bag. Purge reactor three times with H2. Heat to 55°C wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 atmosphere glove bag. In glove bag, add 15.3 mls For safety reasons next two compounds are added in a N_2 of product 4 in reactor base. Add 160 mls ethanol. stirred mini reactor. Place 9.68 gms (0.0204 moles)

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mixture over a bed of celite washing well with ether. water. Dry organic layer with MgSO, filter and desired product and intermediate. Filter reaction progress of run by TLC. Reaction is a mixture of Rotovap and redissolve with ether. Extract with

converted to the desired product. Cool and vent H_2 After second run all of the material has been reactor and run overnight under same conditions.

Reaction is done in a 300 ml stainless steel Parr

conditions.

rotovap to dryness. Dry on vacuum line. Cool reactor and vent H2. Purge with N2. Check

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Charge reactor again with same amounts, seal

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dryness. Dry on vacuum line. Obtain NMR and mass organic layer with MgSO4, filter and rotovap to Dissolve with ether and extract with water. Dry washing well with ether. Rotovap to dryness. pressure. Purge with N₂. Filter over a bed of celite, apec (m/z=474).

Step 6

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flask with magnetic stir bar. Fit flask with N, inlet N_1 purge. Slowly add 2.55 gms potassium t-butoxide NMR and mass spec (m/z=474). rotovap to dryness. Crystallize from ether. Obtain ether. Dry organic layer with MgSO, filter and 10% HCl stirring 10 min. Extract three times with complete, continue to stir at -10°C monitoring by TLC (0.227 mole Aldrich 15,667-1). After addition is and stopper. Chill solution with ice/salt bath under 135 mls anhydrous THF. Place in a 250 ml round bottom Once reaction is complete, quench by adding 135 mls Dissolve 8.97 gms (0.0189 mole) of product 5 with

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Step 7

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C,4H,7NO,S fw=459.65

Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with Ninlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N; purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

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Chill solution with ice bath. Quench with 100 mls 10% K₂CO, while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl, once H₂O, and once with saturated NaCl solution. Dry organic layer with MgSO,, filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec (m/z=460).

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C32H48NO.SI Ew=701.71

Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 60% disp. in mineral oil) in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N, inlet and stopper. Chill NaH with ice bath and begin N, burge.

Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 mls anhydrous DMP. Add to the cold NaH. Stir at cold temperature for 30 min. Add 1.33 gms K₂CO₂ (9.57 mmoles Fisher P-208).

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Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane (43.5 tmmoles Aldrich 33,343-3) with 60 mls anhydrous DMF. Add to cold reaction mixture. Warm to room temperature then heat to 40°C overnight under N₁. Cleanup by diluting with ether and extracting

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sequentially with 5% NaOH, H,O, and saturated NaCl. Dry organic layer with MgSO, filter and dry. Obtain pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and mass spec (m/z=702).

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C13H53N2O6SI fw=802.90

acetonitrile. Purge well with N_2 then close system . usually complete in 48 hrs. Heat at 45°C. Monitor reaction by TLC. Reaction is Aldrich 23,962-3) dissolved in 10 mls anhydrous stir bar. Add 2.9 gms triethyl amine (28.6 mmoles Pischer-Porter pressure reaction vessel with magnetic 10 mls anhydrous acetonitrile. Place in a 3 ounce Dissolve 1.0 gms (1.43 mmoles) of product 8 with

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vacuum. Redissolve with anhydrous chloroform and product. Obtain NMR and mass spec (m/z=675). Repeat several times. Dry to obtain crystalline precipitate quaternary ammonium salt with ether. Perform cleanup by removing acetonitrile under

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Step 1. Preparation of 1

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To a solution of 144 g of KOH (2560 mmol) in 1.1 L of

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103.2 g (80%) of 1 as a clear colorless liquid. H NMR 200 mL plug using hexanes (100%) as elutant yielded organic layer was dried over MgSO, and concentrated in and extracted three times with ethyl acetate. The minutes. Poured reaction contents into 1.0 L of water g of methyliodide (80 mL, 1282 mmol) via addition mmol) slowly via addition funnel. Then was added 182 DMSO was added 120 g of 2-bromobenzyl alcohol (641 2H), 7.12 (d, J = 7.45, 1H), 7.50 (8, 1H). funnel. Stirred at ambient temperature for fifteen (CDCl₃) d 3.39 (8, 3H), 4.42 (8, 2H), 7.18-7.27 (m, vacuo. Purified by silica-gel chromatography through a

Step 2. Preparation of 2

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The organic layer was dried over MgSO, and concentrated mixture was stirred at ambient temperature for 18 elutant gave 53.6 g (43 %) of 2 as an orange oil. 'H (Waters Prep-500) using 5% ethyl acetate/hexanes as in vacuo. Purification by silica gel chromatography washed organic layer with 1N HCL and with 1N NaOH. partitioned between ethyl acetate and water, and hoursand then cooled to 10 °C, quenched with water, 125 g 2,5-difluorobenzoyl chloride (708 mmol). The °C and to it was added 6 g of Pd(PPh,), (5.2 mmol) and thirty minutes, allowed to warm to 5 C, cooled to -10 dissolved in 500 ml THF. The mixture was stirred then to it was added 180 g of zinc iodide (566 mmol) (576 mmol). The mixture was stirred for one hour, and in 1.5 L THF was added 240 mL of 2.5 M n-butyl lithium To a cooled (-78 °C) solution of 95 g (472 mmol) of 1

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NMR (CDC1,) d 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H).

Step 3. Preparation of 3

with diethyl ether. Aqueous layer acidified (pH 1) and .25 Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 Added 1 L water to organic residue and extracted twice extracted with methylene chloride, dried organic layer 2.82 Hz, 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, (242.8 mmol) in 250 ml DMF was heated to 100 °C for 18 hours. The reaction was cooled (0 °C) and 60.7 g of X' silica gel chromatography (Waters Prep-500) using 10% sthyl acetate / hexanes as elutant gave 42.9 g (48 %) (the cyclic sulfate compound of example 1397) (242,8 A solution of 53 g (202.3 mmol) of 2 and 11.2 g Li2S refluxed 2 days. Cooled to ambient temperature and of 3 as a yellow oil. H NMR (CDCl,) d 0.86 (t, J = 3.26 Hz and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and (a, 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, J = over MgSO, and condensed in vacuo. Purification by mol) in 50 mL DMF was added. Stirred at ambient cemperature for 18 hours then condensed in vacuo. 2H), 7.69 (d, J = 7.85 Hz, 1H), 7.74 (s, 1H).

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Step 4. Preparation of 4

.43 (d, J = 5.23 Hz, ZH), 4.16 (s, ZH), 4.42 (s, ZH), (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, ..46 (t, J = 5.84 Hz, 1H), 2.81 (8, 2H), 3.38 (8, 3H), To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of quenched with water and warmed to ambient temperature. 3.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), Waters Prep-500) using 10% ethyl acetate/ hexanes as elutant gave 24.2 g (60%) of 4 as a oil. 14 NMR (CDCl,) 7.09 (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 dried the organic layer over MgSO, and condensed in 3 in 200 mL of methylene chloride was added 21.6 g 1 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), collowed by the addition of 22.4 g triethyl silane Partitioned between methylene chloride and water, trifluoromethane sulfonic acid (12.8 mL, 144 mmol) racuo. Purification by silica gel chromatography 7.32 (m, 2H), 7.42 (m, 1H).

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Step 5. Preparation of

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To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of 4 in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water and extracted three times with ethyl acetate. Washed

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organics with 5% HCl (300 mL) and then with brine (300 mL), dired organics over MgSO, and condensed in <u>vacuo</u> to give 23.1 g (96 %) of 5 as a light brown oil. HNMR (CDCl₂) d 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, J = 9.66 Hz and 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, J = 7.46 Hz, 1H), 7.14 (s, 1H), 7.19 (d, J = 7.65 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

Step 6. Preparation of 6

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To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of 5 in 200 mL methylene chloride was added 28.6 g meta cholorperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na,80, partitioned between water and methylene chloride. Dried organic layer over MgSO, and condensed in vacuo to give 24.5 g (98%) of 6 as a light yellow oil. H NNR (CDCl₃) d 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (a, 2H), 3.39 (a, 3H), 4.44 (a, 2H), 4.50 (a, 2H), 6.93 (d, J = 9.07 Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (a, 1H), 9.38 (a, 1H).

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Step 7. Preparartion of 7

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and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (8, 1.80 (m, 2H), 2.98 (e, 8H), 3.37 (e, 3H), 4.41 (e, 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 colorless oil. ${}^{1}H$ NMR (CDCl₁) d 0.85 (t, J = 7.25 Hz, acetate/hexanes gave 21.8 g (84 %) of 7 as a clear chromatography (Waters Prep-500) using 15 % ethyl concentrated in vacuo. Purification by silica gel was cooled to ambient temperature and the contents and heated to 110 °C for 16 hours. The reaction vessel 20 mL of neat dimethyl amine. The vessel was sealed added 100 mL of a 2.0 M solution of dimethyl amine and THF contained in a stainless steel reaction vessel was To a solution of 24.5 g (52.9 mmol) of 6 in 20 mL of 1H), 9.36 (s, 1H). 2H), 4.44 (8, 2H), 6.42 (8, 1H), 6.58 (dd, J = 9.0 Hz 1H), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz,

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Step 8. Preparation of 8

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A solution of 21.8 g (44.8 mmol) of 7 in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium

t-butoxide was added slowly, maintaining the

temperature at <5 °C. Stirred for 30 minutes, then quenched with 50 mL of saturated ammonium chloride. The organic layer was partitioned between ethyl acetate and water, dried over MgSO4 and concentrated in vacuo. Purification by recrystalization from -10% ethyl acetate/hexanes gave 15.1 g of 8 as a white solid. The mother liquor was purified by silica gel chromatography (Waters Prep-500) using 30% ethyl acetate/hexanes as the elutant to give 3.0 g of 8 as white solid. MS (PABLi') m/e 494.6. HRMS (EI') calculated for M+H 487.2756. Found 487.2746.

Step 9. Preparation of 9

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A solution of 2.0 g (4.1 mmol) of 8 in 20 mL of methylene chloride was cooled to -60 °C. 4.1 mL of a 1M solution of boron tribromide was added. Stirred at ambient temperature for thirty minutes. Cooled reaction to -10 °C and quenched with 50 mL of water. The organic layer was partitioned between methylene chloride and water, dried over MgSO, and concentrated in vacuo. Purification by recrystalization from 50% ethyl acetate/methylene chloride gave 1.95 g (89%) of 9 as a white solid. MS (FABH') m/e 537. HRMS (FAB) calculated for M 536.1834. Found 536.1822.

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Step 10. Preparation of 10

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A solution of 1.09 g (2.0 mmol) of 9 and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacuo. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of 10 as an off white solid. MS (FAB') m/e 535.5.

Example 1400

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Step 1

C14H13O2F fw=232.25

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A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N₂ gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N₂. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride

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vacuo.. The crude product was purified by Kugelrohr the layers were separated, and the organic layer was addition funnel while maintaining reflux. After 15 h combined and acidified with concentrated HCl. The with 20% ag. KOH. All 20% ag. KOH solutions were extracted with a solution of potassium hydroxide and poured into H2O (2.5 L). After 20 min. stirring refluxing, the mixture was cooled to room temperature NMR and MS [(M + H) + = 233] confirmed desired (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. 14 distillation to give a clear, colorless oil ether, dried (MgSO₄), filtered and concentrated in acidic solution was extracted three times with ethyl times with toluene. The toluene washes were extracted stirred for 30 min. The mixture was then washed 5 20% aqueous potassium hydroxide, and the mixture was (783.0g/5.000mol) in toluene (750 mL) was added via (720g) in MeOH (2.5 L). The MeOH layer was added to

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Step 2

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A 12-liter, 3-neck round-bottom flask was fitted with purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-phenol mechanical stirrer and N2 gas adaptor. The system was (455.5g/1.961mol) and dimethylformamide were added.

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the product (605.3g, 97% yield). 1H NMR and MS were washed with ${
m H}_2{
m O}$ and saturated aqueous NaCl, dried times with ethyl ether. The combined organic layers mixture was poured into $\rm H_2O$ (4.0 L), and extracted two room temperature, dimethylthiocarbamoyl chloride The solution was cooled to 6 C, and sodium hydride [(M+H) + = 320] confirm desired structure (55.5g/2.197mol) was added slowly. After warming to (MgSO₄), filtered, and concentrated in vacuo to give (242.4g/1.961mol) was added. After 15 h, the reaction

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Step 3

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A 12-liter, round-bottom flask was equipped with ${\rm N}_2$ C14H13OFS fw-248.32

gas adaptor, mechanical stirrer, and reflux condenser.

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25 20. 30 temperature, MeOH (2.0 L) and THF (2.0 L) were added. dissolved in ethyl ether (1.0 L), and extracted with temparature, the mixture was concentrated by rotavap. then heated to reflux for 2 h. After cooling to room mixture was stirred for 64 h. at room temparature and (605.3g/1.895mol) and phenyl ether (2.0kg) were added. methoxybenzyl)-phenyldimethylthiocarbamate was heated to reflux for 4 h. After cooling to room hydroxide (425.9g/7.590mol) was added, and the mixture and the solution was stirred for 15 h. Potassium and the solution was heated to reflux for 2 h. The The system was purged with N_2 . 4-Fluoro-2-(3-

with concentrated HCl, and extracted with ethyl ether. The ether extracts were dried (MgSO,), filtered, and ${\rm H}_2{\rm O}$. The aqueous extracts were combined, acidified concentrated in vacuo to give an amber oil (463.0g, 98% yield). 1H NMR confirmed desired structure.

Step 4

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C25H35O2FS fw=418.61

ether solution was dried $(MgSO_4)$, filtered, and conc'd methoxyethyl ether (1.0 L) were added and the solution was added slowly, and the mixture was allowed to warm has cooled to 0 C. Sodium hydride (9.68g/383.2mmol) concentrated $\rm H_2SO_4$ was added. The aqueous solution methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2to room temparature, 2,2-Dibutylpropylene sulfate The A 5-liter, 3-neck, round-bottom flask was equipped (110.89g/443.6mmol) was added, and the mixture was aqueous solution was washed with ethyl ether, and temperature, and extracted with ethyl ether. The was heated to reflux for 30 min, cooled to room concentrated by rotavap and dissolved in H2O. with N_2 gas adaptor and mechanical stirrer. stirred for 64 h. The reaction mixture was system was purged with N_2 . 4-Fluoro-2-(3-

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in vacuo to give an amber oil (143.94g/85% yield). $^{
m l}{\rm H}$

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NMR and MS [(M + H) + = 419] confirm the desired structure.

Step 5

C25H33O2FS fw=416.59

[140.53g/651.6mmol) was added. After 6 h., CH2Cl2 was added. After 20 min, the mixture was filtered through system was purged with N_2 . The corresponding alcohol 143.94g/343.8mmol) and $\mathrm{CH}_2\mathrm{Cl}_2$ (1.0 L) were added and (110.6g, 77% yield). 1H NWR and MS [(M + H) + = 417] concentrated in vacuo to give a dark yellow-red oil silica gel, washing with CH2Cl2. The filtrate was A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The cooled to 0 C. Pyridinium chlorochromate

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Step 6

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confirm the desired structure.

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C25H33O4FS fw=448.59

solution was cooled to 0 C, and 3-chloroperbenzoic system was purged with N_2 . The corresponding sulfide with N2 gas adaptor and mechanical stirrer. The A 2-liter, 4-neck, round-bottom flask was equipped funnel. The filtrate was washed with 10% aqueous room temperature After 3.5 h, the reaction mixture 30 min, the reaction mixture was allowed to warm to acid (158.21g/531.7mmol) was added portionwise. After desired structure. the product (93.2g, 78% yield). 1H NMR confirmed the $(MgSO_4)$, filtered, and concentrated in vacuo to give ethyl ether. The organic layers were combined, dried K2CO3. An emulsion formed which was extracted with was cooled to 0 C and filtered through a fine fritted (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added.

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Step 7

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C25H33O4FS fw=448.59

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corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) addition funnel. The system was purged with N_2 . The with N_2 gas adaptor, mechanical stirrer, and a powder A 2-liter, 4-neck, round-bottom flask was equipped

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via addition funnel. After 1h, 10% aq/ HCl (1.0 L) toluene/ethyl acetate to give a white solid (33.60g/ by recryst. from 80/20 hexane/ethyl acetate to give a times with ethyl ether, dried $(MgSO_4)$, filtered, and was added. After 1 h, the mixture was extracted three combined yield: 71%). IH NMR confirmed the desired white solid (32.18 g). The mother liquor was concentrated in vacuo. The crude product was purified Potassium tert-butoxide (23.35g/208.1mmol) was added product. concentrated in vacuo and recrystelized from 95/5 were added, and the mixture was cooled to 0 C.

Step 8

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C27H39O4NS fw=473.67

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25 20 corresponding fluoro-compound (28.1g/62.6mmol) was magnetic stirrer. The system was purged with N_2 . The A Fisher porter bottle was fitted with N_2 line and ether. The ether solution was washed with H_2O , and was heated to 60 C. After 20 h, the reaction The mixture was allowed to warm to room temperature CO_2 /acetone bath and added to the reaction vessel. added, and the vessel was sealed and cooled to -78 C. mixture was allowed to cool and was dissolved in ethyl Dimethylamine (17.1g/379mmol) was condensed via a

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saturated aqueous NaCl, dried (MgSO $_4$), filtered, and concentrated in vacuo to give a white solid (28.5g/96% yield). ¹H NMR confirmed the desired structure.

Step 9

C26H3704NS fw=459.64

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A 250-mL, 3-neck, round-bottom flask was equipped with N₂ gas adaptor and magnetic stirrer. The system was purged with N₂. The corresponding methoxy-compound (6.62g/14.0mmol) and CHCl₃ (150 mL) were added. The reaction mixture was cooled to -78 C, and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature After 4 h, the reaction mixture was cooled to 0 C and was quenched with 10* K₂CO₃ (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The CHCl₃ and ether extracts were combined, washed with saturated aqueous NaCl, dried (MgSO₄), filtered, and concentrated in vacuo to give the product (6.27g/98* yield). ¹H NMR confirmed the desired structure.

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Step 10

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In a 250 ml single neck round bottom Flask with stir bar place 2- diethylamineoethyl chloride hydochloride (fw 172.10g/mole) Aldrich DB, 720-1 (2.4 mmol,4.12g), 34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

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In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg, 2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product (previous step) 1.1 g (2.4 mmoles in 5 ml DMF and the ether solution prepared above. Heat to 40C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (SiO2 99% ethyl acetate/1% NH4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec, and H1 NMR)

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Step 11

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placed in 5 ml acetonitrile in a fischer-porter bottle gms. (Mass spec M-I = 587.9, H NMR). desired product is isolated as a precipitate 0.7272 chloroform. Next ether was added to the chloroform evaporated to dryness and redissolved in 5 mls of 558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was solution and the resulting mixture was chilled. The and heated to 45 C for 3 days. The solution was The product from step 10 (0.57gms, 1.02 millimole fw

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Example 1401

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A 12-liter, 4-neck round-bottom flask was equipped

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with reflux condenser, N2 gas adaptor, mechanical

purged with N2. A slurry of sodium hydride

stirrer, and an addition funnel. The system was

the mixture was cooled to 6 C. A solution of 4reaction mixture was heated to reflux (100 C) for 1h. added via addition funnel over a period of 2.5 h. The fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was (126.0g/4.988mol) in toluene (2.5 L) was added, and A solution of 3-methoxybenzyl chloride

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with 20% ag. KOH. All 20% agueous KOH solutions were refluxing, the mixture was cooled to room temperature 20% aqueous potassium hydroxide, and the mixture was extracted with a solution of potassium hydroxide the layers were separated, and the organic layer was and poured into H2O (2.5 L). After 20 min. stirring (783.0g/5.000mol) in toluene (750 mL). was added via times with toluene. The toluene washes were extracted stirred for 30 min. addition funnel while maintaining reflux. After 15 h. (720g) in MeOH (2.5 L). The MeOH layer was added to The mixture was then washed 5

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NMR and MS [(M + H) + = 233] confirmed desired distillation to give a clear, colorless oil vacuo. The crude product was purified by Kugelrohr ether, dried over MgSO4, filtered and concentrated in (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. H

acidic solution was extracted three times with ethyl

combined and acidified with concentrated HCl. The

Step 2

dimethylformamide were added. The solution was cooled A 12-liter, 3-neck round-bottom flask was fitted to 6 C, and sodium hydride (55.5g/2.197mol) was added product (605.3g, 97% yield). 1H NMR and MS [(M+H) + = into ${\rm H}_2{\rm O}$ (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured i_2 0 and saturated aqueous NaCl, dried over MgSO $_4$, filtered, and concentrated in vacuo to give the with mechanical stirrer and N_2 gas adaptor. methoxybenzyl)-phenol (455.5g/1.961mol) and After warming to room temperature, system was purged with N2. 4-Fluoro-2-(3-320] confirm desired structure. slowly.

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Step 3

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nydroxide (425.9g/7.590mol) was added, and the mixture (605.3g/1.895mol) and phenyl ether (2.0kg) were added, mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room A 12-liter, round-bottom flask was equipped with condenser. The system was purged with N2. 4-Fluorotemperature, MeOH (2.0 L) and THF (2.0 L) were added, temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with with conc. HCl, and extracted with ethyl ether. The was heated to reflux for 4 h. After cooling to room H2O. The aqueous extracts were combined, acidified concentrated in vacuo to give an amber oil (463.0g, and the solution was heated to reflux for 2 h. The and the solution was stirred for 15 h. Potassium ether extracts were dried (MgSO,), filtered, and 98% yield). 1H NMR confirmed desired structure. 2-(3-methoxybenzyl)-phenyldimethylthiocarbamate N_2 gas adaptor, mechanical stirrer, and reflux

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Step 4

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C25H35O2FS fw-418.61

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A 5-liter, 3-neck, round-bottom flask was equipped with $\rm N_2$ gas adaptor and mechanical stirrer.

concentrated in vacuo to give an amber oil ether solution was dried (MgSO4), filtered, and conc. H2SO4 was added. The aqueous solution was methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-The system was purged with N2. 4-Fluoro-2-(3confirm the desired structure. temperature, and extracted with ethyl ether. The aqueous solution was washed with ethyl ether, and concentrated by rotavap and dissolved in H_2O . The stirred for 64 h. The reaction mixture was was added slowly, and the mixture was allowed to warm was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) methoxyethyl ether (1.0 L) were added and the solution (143.94g/85% yield). ¹H NMR and MS [(M + H) + = 419] heated to reflux for 30 min, cooled to room (110.89g/443.6mmol) was added, and the mixture was to room temperature 2,2-Dibutylpropylene sulfate

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Step 5

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added and cooled to 0 C. Pyridinium chlorochromate alcohol (143.94 g/343.8 mmol) and CH2Cl2 (1.0 L) were equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N2. The corresponding A 2-liter, 4-neck, round-bottom flask was

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concentrated in vacuo to give a dark yellow-red oil silica gel, washing with CH2Cl2. The filtrate was added. After 20 min, the mixture was filtered through (110.6g, 77% yield). ¹H NMR and MS $\{(M + H)^{+} = 417\}$ (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was confirm the desired structure.

Step 6

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25 20 15 equipped with N2 gas adaptor and mechanical stirrer. concentrated in vacuo to give the product (93.2g, 78% through a fine fritted funnel. The filtrate was sulfide (110.6g/265.5mmol) and CH2Cl2 (1.0 L) were The system was purged with N2. The corresponding yield). $^{
m L}$ H NMR confirmed the desired structure. layers were combined, dried (MgSO4), filtered, and washed with 10% aqueous K2CO3. An emulsion formed chloroperbenzoic acid (158.21g/531.7mmol) was added added. The solution was cooled to 0 C, and 3which was extracted with ethyl ether. The organic reaction mixture was cooled to 0 C and filtered allowed to warm to room temperature After 3.5 h, the portionwise. After 30 min, the reaction mixture was A 2-liter, 4-neck, round-bottom flask was

C25H33O4FS fw=448.59

added via addition funnel. After 1h, 10% aq/ HCl (1.0 equipped with N_2 gas adaptor, mechanical stirrer, and THF (1.0 L) were added, and the mixture was cooled to three times with ethyl ether, dried (MgSO4), filtered from 95/5 toluene/ethyl acetate to give a white solid a powder addition funnel. The system was purged with 0 C. Potassium tert-butoxide (23.35g/208.1mmol) was (33.60g, combined yield: 71%). $^1\mathrm{H}$ NMR confirmed the N_2 . The corresponding aldehyde (93.2g/208mmol) and L) was added. After 1 h, the mixture was extracted cetate to give a white solid (32.18g). The mother iquor was concentrated in vacuo and reciystsilized purified by recrystallized from 80/20 hexane/ethyl and concentrated in vacuo. The crude product was A 2-liter, 4-neck, round-bottom flask was desired product.

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Step 8

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C27H3904NS fw=473.67

A Fisher porter bottle was fitted with N₂ line and magnetic stirrer. The system was purged with N₂. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a CO₂/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethylether. The ether solution was washed with H₂O, saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated in vacuo to give a white solid (28.5g/96% yield). ¹H NMR confirmed the desired structure.

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Step 10

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Step 9

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C26H37O4NS fw=459.64

yield). IH NMR confirmed the desired structure. concentrated in vacuo to give the product (6.27g/98% aqueous NaCl, dried over $MgSO_4$, filtered, and ether extracts were combined, washed with saturated extracted two times with ethyl ether. The CHCl3 and 4 h, the reaction mixture was cooled to 0 C and was mixture was allowed to warm to room temperature After boron tribromide (10.50g/41.9mmol) was added. The compound (6.62g/14.0mmol) and CHCl3 (150 mL) were was purged with N_2 . The corresponding methoxywith ${
m N}_2$ gas adaptor and magnetic stirrer. The system layers were separated, and the aqueous layer was quenched with 10% K_2CO_3 (100 mL). After 10 min, the added. The reaction mixture was cooled to -78 C, and

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A 250-mL, 3-neck, round-bottom flask was equipped

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ether extraction and dry over anhydrous potassium millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N carbonate. stir bar place 2- diethylamineoethyl chloride KOH (aqueous). Stir 15 minutes and then separate by hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 In a 250 ml single neck round bottom flask with

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mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool 5% NaOH, followed by water and then brine. The ether was diluted with ether and extracted with 1 portion of with stir bar add sodium hydride (60% dispersion in Isolated yield: 0.78 g (mass spec , and H1 NMR) product may be further purified by chromatography removing ether by rotary evaporation (1.3 gms). The layer was dried over Magnesium sulfate and isolated by product which contained no starting material by TLC solution prepared above. Heat to 40C for 3 days. The step) 1.1 g (2.4 mmol in 5 ml DMF and the ether to ice temperature. Next add phenol product (previous (silica 99% ethyl acetate/1% NH4OH at 5ml/min.). In a separate 2-necked 250 ml round bottom flask

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Step 11

The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and iodoethane (1.6 gms (10.02 mmillimoles) was place in 5 ml acetonitrile in a Pischer-Porter bottle and heated to 45 C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was rolloroform solution and the resulting mixture was rollided. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9, ¹H

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Example 1402

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(4R-cis) -5-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-bydroxy-1,1-dioxido-1benzothlepin-5-yl]phenoxy]pontyl]thio]-lH-totrasole-1acotic acid

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Step 1. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol

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solid: 'H NMR (CDCl,) & 3.79 (s, 3H), 3.90 (s, 2H), 4.58 evolution stopped. The mixture was cooled down to room hydride (0.94 mol) in 600 mL of dry toluene was added with 500 mL of water. The organic layer was separated, through a layer of 1 L of silica gel with neat hexane dried over MgSO,, and concentrated under high vacuum. (8, 1H), 6.70-6.74 (m, 1H), 6.79-6.88 (m, 4H), 7.11coluene was added. After refluxing for 24 hours, the To a stirred solution of 23.66 g of 95% sodium mixture was cooled to room temperature and quenched to yield 53.00 g (25.6%) of the product as a pink methoxybenzyl chloride (0.89 mol) in 400 mL of dry distillation. The crude dark red oil was filtered mixture was stirred at 90°C for 1 hour until gas The remaining starting materials were removed by .00.0 g of 4-fluorophenol (0.89 mol) at 0°C. The temperature and a solution of 139.71 g of 3-7.16 (m, 2H).

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Step 2. Preparation of 4-fluoro-2-((4methoxyphenyl)methyl)-thiophenol

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Step 2a. Preparation of thiocarbamate

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To a stirred solution of 50.00 g (215.30 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol in 500 mL of dry DMF was added 11.20 g of 60% sodium hydride dispersion in mineral oil (279.90 mmol) at 2°C. The mixture was allowed to warm to room temperature and 26.61 g of dimethylthiocarbamoyl chloride (215.30 mmol)

3H), 6.90-7.00 (m, 2H), 7.09 (d, J = 8.7 Hz, 2H). 3.46 (s, 3H), 3.80 (s, 3H), 3.82 (s, 2H), 6.78-6.86 (m, as a pale white solid: 'H NMR (CDCl₁) § 3.21 (s, 3H), acetate/hexane to yield 48.00 g (69.8%) of the product stripped to dryness. The crude product was filtered brine. The ether solution was dried over MgSO, and extracted with 500 mL of diethyl ether. The ether 100 mL of water in an ice bath. The solution was temperature overnight. The mixture was quenched with was added. The reaction mixture was stirred at room through a plug of 500 mL silica gel using 5% ethyl solution was washed with 500 mL of water and 500 mL of

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to 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol Step 2b. Rearrangement and hydrolysis of thiocarbamate

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4.07 (8, 2H), 6.82-6.86 (m, 3H), 6.93 (dt, J = 8.4 Hz 2.7 Hz, 1H), 7.08 (d, $\underline{J} = 8.7$ Hz, 2H), 7.49 (dd, $\underline{J} =$ washed with 5% ethyl acetate/hexane to give 46.00 g diphenyl ether was refluxed at 270°C overnight. The 6.0 Hz, 8.7 Hz, 1H). to remove phenyl ether. The rearrangement product was filtered through 1 L of silica gel with 2 L of hexane thiocarbamate (obtained from Step 2a) in 200 mL of (CDC1,) & 3.02 (8, 3H), 3.10 (8, 3H), 3.80 (8, 3H), (95.8%) of the product as a pale yellow solid: 'H NMR solution was cooled down to room temperature and A stirred solution of 48.00 g (150.29 mmol) of

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200 mL of THF was added 17.28 g of NaOH (432.06 mmol). diethyl ether twice and placed in an ice bath. The solvents were evaporated off and 200 mL of water was The mixture was refluxed under nitrogen overnight. The HCl solution. The solution was extracted with 300 mL of aqueous mixture was acidified to pH 6 with concentrated rearrangement product (above) in 200 mL of methanol and To a solution of 46.00 g (144.02 mmol) of the The aqueous solution was washed with 200 mL of

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6.81-6.87 (m, 4H), 7.09 (d, J = 8.7 Hz, 2H), 7.27-7.33 27.00 g (75.5%) of the product as a brown oil: 'H NMR dried over MgSO, and stripped to dryness to afford diethyl ether twice. The ether layers were combined (CDCl₁) § 3.24 (s, 1H), 3.80 (s, 3H), 3.99 (s, 2H),

Step 3. Preparation of dibutyl cyclic sulfate Preparation of 2,2-dibutyl-1,3-propanediol.

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product. 98.4 g (yield 95%) as an oil. MS spectra and proton ml of water were added dropwise. The resulting stirred at RT overnight. The reaction was cooled to and carbon NMR spectra were consistent with the sodium sulphate and concentrated in vacuo to give diol suspension was filtered. The filtrate was dried over 20°C and 40 ml of water, and 80 mL of 10% NaOH and 80 temperature between -20 to 0°C. The reaction was acetone/dry ice bath was added LAH (1 M THF) 662 ml (1.2 eq., 0.66 mol) dropwise maintaining the (Aldrich) (150g, 0.55 mol in dry THF (700ml) in an To a stirred solution of di-butyl-diethylmalonate

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Step 3b. Preparation of dibutyl cyclic sulfite

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0.548 mol, obtained from Step 3a) and triethylamine with brine twice. The organic phase was dried over and within 5 min the solution turned yellow and then magnesium sulfate and concentrated under vacuum to give 0°C. GC showed that there was no starting material hour. The reaction mixture was stirred for 3 hrs. at black when the addition was completed within half an thionyl chloride (97.8 g, 0.82 mol) was added dropwise ml) was stirred at 0°C under nitrogen. To the mixture, left. The mixture was washed with ice water twice then (221 g, 2.19 mol) in anhydrous methylene chloride (500 A solution of 2,2-dibutyl-1,3-propanediol (103 g,

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128 g (100%) of the dibutyl cyclic sulfite as a black oil. Mass spectrum (MS) was consistent with the product.

Oxidation of dibutyl cyclic sulfite to Step 3c.

dibutyl cyclic sulfate

To a solution of the dibutyl cyclic sulfite (127.5 under nitrogen was added ruthenium (III) chloride (1 g) acetonitrile and 500 ml of water cooled in an ice bath ath brine. The organic phase was dried over magnesium concentrated under vacuum and to give 133 g (97.8%) of and sodium periodate (233 g, 1.08 mol). The reaction of ether and the ether extract was washed three times material left. The mixture was extracted with 300 ml sulfate and passed through celite. The filtrate was was stirred overnight and the color of the solution carbon NMR and MS were consistent with the product. turned black. GC showed that there was no starting the dibutyl cyclic sulfate as an oil. Proton and g, 0.54 mol, obtained from Step 3b) in 600 ml

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3tep 4. Preparation of aryl-3-hydroxypropylsulfide

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added 25 mL of concentrated sulfuric acid to make a 2.0 To a stirred solution of 27.00 g (108.73 mmol) of 1.35 g of 60% sodium hydride dispersion in mineral oil for 10 minutes. The mixture was allowed to warm up to obtained from Step 2) in 270 mL of diglyme was added (obtained from Step 3c) was added at 0°C and stirred solution was washed with 200 mL of diethyl ether and M solution that was refluxed overnight. The solution room temperature and stirred overnight. The solvent 29.94 g (119.60 mmol) of the dibutyl cyclic sulfate (108.73 mmol) at 0°C. After gas evolution ceased, was evaporated and 200 mL of water was added. The solution was dried over MgSO, and concentrated in was extracted with ethyl acetate and the organic 4-fluoro-2-((4-methoxyphenyl)methyl)thiophenol

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purified by silica gel chromatography (Waters Prep 500) using 8% ethyl acetate/hexane to yield 33.00 g (72.5%) 0.90 (t, J = 7.1 Hz, 6H), 1.14-1.34 (m, 12H), 2.82 (s, 6.92 (m, 4H), 7.09 (d, <u>J</u> = 8.7 Hz, 2H), 7.41 (dd, <u>J</u> = of the product as a light brown oil: 'H NMR (CDCl,) & 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10 (s, 2H), 6.77vacuo. The crude aryl-3-hydroxypropylsulfide was 3.7 Hz, 5.7 Hz, 1H). Step 5. Preparation of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

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1 - 13.5 Hz, 1H), 3.45 (d, J - 12.3 Hz, 1H), 3.69 (d, J aryl-3-hydroxypropylsulfide (obtained from Step 4) in 1 IH), 6.83-6.93 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 7.18enantiomerically-enriched aryl-3-hydroxypropyleulfoxide 1.16-1.32 (m, 12H), 2.29 (d, J = 13.8 Hz, 1H), 2.77 (d, and the crude solid was washed with 1 L of hexane. The as a colorless oil: ¹H NMR (CDCl₁) & 0.82-0.98 (m, 6H), L of methylene chloride was added 31.50 g of 96% (1R)-7.23 (m, 1H), 7.99-8.04 (m, 1H). Enantiomeric excess 30°C freezer for 72 hours. The solvent was evaporated To a stirred solution of 20.00 g (47.78 mmol) of oxaziridine dissolved the mixture was placed into a was concentrated in vacuo. The crude oil was purified white solid was filtered off and the hexane solution ethyl acetate/hexane to afford 19.00 g (95%) of the = 12.3 Hz, 1H), 3.79 (8, 3H), 4.02 (q, <u>J</u> = 15.6 Hz, on a silica gel column (Waters Prep 500) using 15% (-) - (8,8-dichloro-10-camphor-sulfonyl) oxaziridine (100.34 mmol, Aldrich) at 2°C. After all the

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was determined by chiral HPLC on a (R,R)-Whelk-O column using 5% ethanol/hexane as the eluent. It showed to be 18% e.e. with the first eluting peak as the major product.

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Step 6. Preparation of enantiomerically-enriched aryl-3-propanalsulfoxide

7.03 (d, J = 8.4 Hz, 2H), 7.19 (dt, J = 8.4 Hz, 2.4 Hz, 1.11-1.17 (m, 4H), 1.21-1.39 (m, 4H), 1.59-1.76 (m, Hz, 1H), 4,12 (d, $\underline{J} = 15.9 \text{ Hz}$, 1H), 6.84-6.89 (m, 3H), 4H), 1.89-1.99 (m, 1H), 2.57 (d, J = 14.1 Hz, 1H), 2.91 enantiomerically-enriched aryl-3-propanalsulfoxide as a ethyl acetate/hexane to give 17.30 g (91%) of the oil was filtered through 500 mL of silica gel using 15% dried over MgSO,, and concentrated in vacuo. The crude acetate twice. The ethyl acetate layer was separated, water was added to the mixture and stirred vigorously. Step 5) and 20.96 g of sulfur trioxide-pyridine (131.16 were added 19.00 g (43.72 mmol) of enantiomerically-1H), 8.02 (dd, J = 8.7 Hz, 5.7 Hz, 1H), 9.49 (8, 1H). (d, $\underline{J} = 13.8 \text{ Hz}$, 1H), 3.79 (8, 3H), 3.97 (d, $\underline{J} = 15.9$ light orange oil: 1H NMR (CDCl₃) δ 0.85-0.95 (m, 6H), was stirred at room temperature for 48 hours, 500 mL of mmol, Aldrich) at room temperature. After the mixture enriched aryl-3-hydroxypropylsulfoxide (obtained from (131.16 mmol, Aldrich) in 200 mL dimethyl sulfoxide The mixture was then extracted with 500 mL of ethyl To a stirred solution of 13.27 g of triethylamine

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Step 7. Preparation of the enantiomerically-enriched tetrahydrobenzothlepine-1-oxide (4R, 5R)

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To a stirred solution of 17.30 g (39.99 mmol) of enantiomerically-enriched aryl-3-propanalsulfoxide (obtained from Step 6) in 300 mL of dry THF at -15°C was added 48 mL of 1.0 M potassium t-butoxide in THF (1.2 equivalents) under nitrogen. The solution was stirred at -15°C for 4 hours. The solution was then quenched with 100 mL of water and neutralized with 4 mL of concentrated HCl solution at 0°C. The THF layer was separated, dried over MgSO, and concentrated in vacuo. The enantiomerically-enriched tetrahydrobenzothiepine-

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1-oxide (4R,5R) was purified by silica gel chromatography (Waters Prep 500) using 15% ethyl acetate/hexane to give 13.44 g (77.7%) of the product as a white solid: 'H NNMR (CDCl₂) & 0.87-0.97 (m, 6H), 1.16-1.32 (m, 4H), 1.34-1.48 (m, 4H), 1.50-1.69 (m, 4H), 1.86-1.96 (m, 1H), 2.88 (d, <u>J</u> = 13.0 Hz, 1H), 3.00 (d, <u>J</u> = 13.0 Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), 4.48 (s, 1H), 6.52 (dd, <u>J</u> = 9.9 Hz, 2.4 Hz, 1H), 6.94 (d, <u>J</u> = 9 Hz, 2H), 7.13 (dt, <u>J</u> = 8.7 Hz, 2H, 7.38 (dd, <u>J</u> = 8.7 Hz, 5.7 Hz, 1H). Step 8. Preparation of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

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6.96-7.07 (m, 3H), 7.40 (d, J = 8.1 Hz, 2H), 8.11 (dd 1H), 5.48 (8, 1H), 6.54 (dd, $\underline{J} = 10.2 \text{ Hz}$, 2.4 Hz, 1H), δ 0.89-0.95 (m, 6H), 1.09-1.42 (m, 12H), 2.16-2.26 (m, 50 mL of saturated NaHCO, solution. chloride was added 9.46 g of 68% m-chloroperoxybenzoic J = 8.6 Hz, 5.9 Hz, 1H1H), 3.14 (q, J = 15.6 Hz, 1H), 3.87 (8, 3H), 4.18 (8, dioxide (4R,5R) as a light yellow solid: 'H NMR (CDCl,) concentrated in vacuo to give 13.00 g (97.5%) of the chloride layer was separated, dried over MgSO, and saturated Na,SO, was added into the mixture and stirred acid (37.28 mmol, Sigma) at 0 °C. After stirring at 0 oxide (obtained from Step 7) in 150 mL of methylene enantiomerically-enriched tetrahydrobenzothiepine-1enantiomerically-enriched tetrahydrobenzothiepine-1,1for 30 minutes. The solution was then neutralized with room temperature and stirred for 4 hours. 50 mL of °C for 2 hours, the mixture was allowed to warm up to To a stirred solution of 13.44 g (31.07 mmol) of The methylene

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Step 9. Preparation of enantiomerically-enriched 7-[dimethylamino]tetrahydrobenzothiepine-1,1-dioxide [4R,5R]

To a solution of 13.00 g (28.98 mmol) of

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I = 8.4 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). The product 3.7 Hz, 2.4 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.42 (d, remaining solution was concentrated and recrystallized give 9.8 g of colorless solid. Enantiomeric excess enantiomerically-enriched tetrahydrobenzothiepine-1,1-Prep 500) using 20% ethyl acetate/hexane gave 12.43 g 2.81 (8, 6H), 2.99 (d, J = 15.3 Hz, 1H), 3.15 (d, J = 15.3 Hz, 1H), 3.84 (B, 3H), 4.11 (d, J = 7.5 Hz, 1H), 5.49 (B, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = the mixture was sealed and stirred at 110°C overnight, Reactor was added about 20 mL of neat dimethylamine. 100 mL of water, dried over MgSO, and concentrated in dissolved in 200 mL of ethyl acetate and washed with (4R,5R) as a colorless solid: 'H NMR (CDCl,) & 0.87-3.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), was determined to have 78% e.e. by chiral HPLC on a vacuo. Purification on a silica gel column (Waters eluent. Recrystallization of this solid from ethyl acetate/hexane gave 1.70 g of the racemic product. (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide Chiralpak AD column using 5% ethanol/hexane as the Chiralpak AD column using 5% ethanol/hexane as the eluent. It showed to have 96% e.e with the first of this solid was determined by chiral HPLC on a dimethylamine was evaporated. The crude oil was dimethylamine (2.0 M in THF, 146 mmol) in a Parr and cooled to ambient temperature. The excess (90.5%) of the enantiomerically-enriched 7dioxide (obtained from Step 8) in 73 mL of sluting peak as the major product.

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(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide Step 10: Demethylation of 5-(4'-methoxyphenyl)-7-(4R, SR)

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297 mmol), and the resulting solution was stirred cold ice bath at -10 °C, and slowly quenched with 300 mL of dioxide (obtained from Step 9) in 500 mL of methylene To a solution of 47 g (99 mmol) of enantiomericenriched (dimethylamino) tetrahydrobenzothiepine-1,1complete. The reaction was cooled in an acetone-dry water. The mixture was warmed to 10 °C, and further boron tribromide (297 mL, 1M in methylene chloride, (-5 °C to 0 °C) for 1 hour or until the reaction was chloride at -10 °C was added dropwise a solution of

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concentrated in vacuo to give the crude 4-hydroxyphenyl solution to neutralize the mixture. The aqueous layer temperature. The mixture was washed twice with 200 mL concentrated in vacuo. The residue was dissolved in was separated and extracted with 300 mL of methylene chloride, and the combined extracts were washed with intermediate. The solid residue was recrystallized diluted with 300 mL of saturated sodium bicarbonate from methylene chloride to give 37.5 g (82%) of the 500 mL of ethyl acetate and stirred with 50 mL of of water, 200 mL of brine, dried over MgSO, and glacial acetic acid for 30 minutes at ambient 200 mL of water, brine, dried over MgSO, and desired 5-(4'-hydroxyphenyl)-7-

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white solid: ¹H NMR (CDCl₃) 80.84-0.97 (m, 6H), 1.1-1.5 Hz, 1H), 6.55 (dd, J = 9, 2.4 Hz, 1H), 6.88 (d, 8,7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 9 Hz, 2H). (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide as (8, 6H), 3.00 (d, J = 15.3 Hz, 1H), 3.16 (d, J = 15.3 Hz, 1H), 4.11 (8, 2H), 5.48 (8, 1H), 6.02 (d, J = 2.4(m, 10H), 1.57-1.72 (m, 1H), 2.14-2.28 (m, 1H), 2.83

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Alternatively, enantiomeric-enriched 5-(4'. hydroxyphenyl) -7-

(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide, the intermediate just described, can be prepared via non-

hydroxypropylsulfide (obtained from Step 4) with menantioselective synthesis followed by chiral conditions as in Step 7 and Step 9) to give the racemic in Step 8, but with 2.2 equivalent of m-CPBA) gave the chromatography separation. 5- (4'-hydroxyphenyl)-7through the synthetic sequences (under the same racemic sulfone intermediate. The sulfone was carried chloroperbenzoic acid (under the similar conditions as Oxidation of aryl-3-

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desired enantiomeric-enriched 5-(4'-hydroxyphenyl)-7appropriate chiral chromatographic purification. The two enantiomers were further separated into the (dimethylamino) tetrahydrobenzothiepine-1, 1-dioxide by (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide

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Step 11: Preparation of ester intermediate

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0.88-0.94 (m, 6H), 1.13-1.46 (m, 10H), 1.60-1.64 (m, 1.30g (98%) of the ester intermediate: 1H NMR (CDCl₃) & sulfate, filtered and the solvent evaporated to afford added to the reaction mixture, extracted with ethyl dimethylformamide was added 60 mg (2.38 mmol) of 95% 7.37 (B, SH), 7.42 (d, J = 8.5 Hz, 2H), 7.93 (d, J = Hz, 1H), 3.16 (t, J = 15.1 Hz, 1H), 4.11 (8, 1H), 5.26 1H), 2.20-2.24 (m, 1H), 2.81 (8, 6H), 3.00 (d, J = 15.1 acetate, washed with brine, dried over magnesium 2-bromoacetate and stirred for two hours. Water was reaction mixture was added 400 µL (2.52 mmol) of benzyl thiepine-1,1-dioxide (obtained from Step 10) in 10 mL (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), sodium hydride and stirred for 15 minutes. To the hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-(8, 2H), 5.49 (8, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.63To a solution of 1.0 g (2.18 mmol) of 5-(4'-

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Step 12: Preparation of acid

C3.H4.NO.S: 518.2576. Found: 518.2599. 8.5 Hz, 2H), 7.97 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for J = 9.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz1H), 4.72 (s, 2H), 5.51 (s, 1H), 6.17 (s, 1H), 6.74 (d, J = 15.1 Hz, 1H), 3.17 (t, J = 14.9 Hz, 1H), 4.12 (s,1.65 (m, 1H), 2.17-2.21 (m, 1H), 2.85 (8, 6H), 3.02 (d, compound as a white solid: mp 119 - 123 °C; 'H NMR the solvent was evaporated to afford the desired title The reaction mixture was filtered through celite and atmosphere of hydrogen gas (40 psi) for three hours. with 10% palladium on carbon was placed under an intermediate (obtained from Step 1) in 40 mL ethanol (CDCl₃) 8 0.89-0.94 (m, 6H), 1.19-1.43 (m, 10H), 1.61-A solution of 1.30 g (2.14 mmol) of ester

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Example 1403

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yl]phenoxyacetyl]glycine tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-(4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamine)-2,3,4,520

Step 1: Preparation of glycine ester intermediate

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thiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-To a solution of 6.4 g (13.9 mmol) of 5-(4'-

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to reflux for 2 days, cooled to ambient temperature and (90%) of glycine ester intermediate as a white foam: "H (chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) Purification by silica gel chromatography (Waters Prep-(d, J = 8.5 Hz, 2H), 7.17 (B, 1H), 7.47 (d, J = 8.3 Hz, of tetrabutylammonium iodide. The reaction was heated (m, 6H), 4.25 (q, J = 7.0 Hz, 2H), 4.57 (8, 2H), 5.50 (8, 1H), 5.98 (8, 1H), 6.56 (d, J = 8.6 Hz, 1H), 6.98 acetate and water. The organic layer was washed with 3.08 (ABq, Jas = 15.3 Hz, J = 48.9 Hz, 2H), 4.06-4.19 stirred for 20 hours, then partitioned between ethyl NMR (CDCl,) & 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 500) using 50% ethyl acetate/hexanes afforded 7.5 g 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), orine, dried over MgSO,, and concentrated in vacuo. ml of acetone was added 3.8 g (21.0 mmol) of N-2H), 7.91 (d, J = 8.7 Hz, 1H).

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Step 2: Preparation of acid

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21.6 Hz, 2H), 4.01 (8, 2H), 4.07 (8, 1H), 4.61 (8, 2H), recrystallization from ethyl acetate gave 5.45 g (78%) Intermediate (obtained from Step 1) and 1.5 g LiOH.H,O 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 5.31 (8, 1H), 6.04 (8, 1H), 6.57 (d, J = 9.0 Hz, 1H), A solution of 7.3 g (12.1 mmol) of glycine ester organic layer was washed with brine, dried over MgSO., of the desired title compound as a white crystalline neated to 45 °C for 2 hours. This was then cooled to mp 149-150 °C; ¹H NMR (CD₃OD) δ 0.88-0.98 (m, (m, 1H), 2.79 (s, 6H), 3.11 (ABq, JAs = 15.3 Hz, J = 7.08 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), (36.3 mmol) in 60 mL of THF and 60 mL of water was partitioned between ethyl acetate and water. The 7.76 (d, J = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS (ES+) ambient temperature, acidified with 1 N HCl and and concentrated in vacuo. Purification by 3011d:

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Calc'd for C₁₀H₁₃N₂O₅: 575.2712. Found: 575.2790. Anal. Calc'd for: C₁₀H₁₃N₂O₅S C, 62.69; H, 7.37; N, 4.87. Found: C, 62.87; H, 7.56; N, 4.87.

Example 1404

(4R-cis)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-4-bydroxy-1,1-dioxido-1-bensothiepin-5yllphenoxy]pentanoic acid

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Step 1: Preparation of ester intermediate

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J = 7.9 Hz, 1H), 5.13 (8, 2H), 5.47 (8, 1H), 6.00 (d, J (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (1.0 6H), 3.05 (ABq, J = 15.1 Hz, J = 47.7 Hz, 2H), 4.10 (d, 1H), 1.86 (m, 2H), 2.21 (m, 1H), 2.47 (m, 2H), 2.81 (8, (CDC1,) 8 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.64 (m, or 24 hours. The pale amber slurry was cooled to 25 residue. Purification by flash chromatography (2.4 x 30 cm silica, 20-40% EtOAc/hexane) afforded the ester Intermediate (1.2 g, 86%) as a colorless oil: 'H NMR g, 2.2 mmol, obtained from Example 1402, Step 10) in ng), and the resulting solution was stirred at 65 °C C and was concentrated in vacuo to provide a yellow powdered K,CO, (0.45 g, 3.3 mmol, 1.5 eq.), benzyl 5catalytic amount of tetra-n-butylammonium iodide (2 acetone (10 mL) at 25 °C under N, was treated with promovalerate (0.88 g, 3.3 mmol, 1.5 eq.) and a A solution of 5-(4'-hydroxyphenyl)-7-

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2H), 7.86 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for J = 8.7 Hz, 2H, 7.36 (m, 5H), 7.40 (d, J = 8.5 Hz,= 2.5 Hz, 1H), 6.50 (dd, J = 8.9, 2.5 Hz, 1H), 6.91 (d, C16H51NO6S: 650.3515. Found: 650.3473.

Step 2: Preparation of acid

7.84 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for C11H4NO68: ■ 8.7 Hz, 2H), 7.39 (m, 5H), 7.39 (d, J = 8.3 Hz, 2H), 4.00 (8, 2H), 4.09 (8, 1H), 5.45 (8, 1H), 5.99 (d, J =2.81 (8, 6H), 3.05 (ABq, J = 15.1 Hz, J = 49.7 Hz, 2H), 1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), compound (0.54 g, 63%) as a white foam: mp: 76-79 °C; concentrated in vacuo to give a white foam. the reaction mixture for 10 min. wt %) then stirred under an atmosphere (1 atm) of H_3 560.3046. Found: 560.3043. 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J'H NMR (CDCl) 8 0.90 (m, 6H), 1.10-1.46 (br m, 10H), silica, 1.5% BtOH/CH₂Cl₂) afforded the desired title Purification by flash chromatography (2.6 x 25 cm bubbled through the slurry for 1 min, for a total via hydrogen balloon. Every 10 min, hydrogen gas was °C was treated with 5% palladium on carbon (0.15 g, 10 mmol, obtained from Step 1) in ethanol (7.5 mL) at 25 filtered through a plug of Celite (10 g) and an atmosphere of N, and nitrogen was bubbled through reaction time of 4 hours. The slurry was placed under A solution of the ester intermediate (0.99 g, 1.5 The mixture was

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yl)phenoxy-1-butanesulfonamide tetrahydro-4-hydroxy-1,1-dioxido-1-bensothiepin-5-(4R-cis)-4-(4-(3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-

20 15 30 25 10 sulfonic acid as colorless needles: mp 229-236 °C recrystallized from CH₂CN/hexane to give the desired provide 8.8 g (92%) of the desired sulfonic acid as a filtered and washed with water and dried in vacuo to additional 16 h. The resultant white precipitate was mixture was vigorously stirred for 4 h then allowed to solution cooled to 0 °C over a 30 min period. The colorless solution was added dropwise to a 4 N HCl homogeneous mixture was obtained. The clear and quenched by the addition of water (50 mL), until a 1.5 equiv.) and stirred and heated at 65 °C for 64 h. 1.5 equiv.) and 1,4-butane sultone (2.5 mL, 24.1 mmol, with powdered potassium carbonate (3.3 g, 24.1 mmol, 10) in acetone (35 mL) at 25 °C under N, was treated thiepine-1,1-dioxide (obtained from Example 1402, Step hydroxyphenyl) -7- (dimethylamino) tetrahydrobenzo-Step 1: Preparation of sulfonic acid intermediate warm to ambient temperature and stirred for an white solid. A portion of the white solid was The solution was allowed to cool to 25 °C and A solution of 7.4 g (16.1 mmol) of 5-(4'-

(decomposed); ¹H NMR (DMSO-d₄) & 0.82 (m, 6H), 1.02-1.33 (br m, 10H), 1.59 (m, 1H), 1.73 (m, 4H), 2.00 (s, 1H), 2.48 (m, 2H), 2.71 (s, 6H), 2.98 (s, 1H), 3.86 (s, 1H), 3.93 (m, 2H), 5.08 (s, 1H), 5.89 (s, 1H), 6.52 (dd, J = 8.9, 2.4 Hz, 1H), 6.92 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.9 Hz, 1H); Anal. Calc'd for C₃₀H₄NO₃, C, 60.48; H, 7.61; N, 2.35. Found: C, 60.53; H, 7.70; N, 2.42.

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Step 2: Preparation of 7-(dimethylamino)benzothiepin-5-yl]phenoxy-1-butanesulfonamide

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(125 mg, 11%): mp 108-110 °C; H NMR (CDCl1) 8 0.85-0.93 2.20 (m, 5H), 2.82 (s, 6H), 2.99 (d, J = 15.3 Hz, 1H), solvent evaporated. To the residue was added 30 mL of 2H), 5.47 (B, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.52 (dd, and washed with brine. Dried with MgSO,, filtered and The residue was purified by MPLC (33% EtOAc in hexane) to afford the desired title compound as a beige solid (m, 6H), 1.13-1.59 (m, 10H), 1.60-1.67 (m, 1H), 1.94-4.03 (t, J = 5.8 Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (B, (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.9 Hz, 1H). HRMS. J = 8.9, 2.6 Hz, 1H), 6.91 (d, J = 8.9 Hz, 2H), 7.41 3.15 (t, J = 15.3 Hz, 1H), 3.23 (t, J = 7.7 Hz, 2H), nour. Water was added and the mixture was extracted precipitate was filtered and the solvent evaporated. sulfonic acid (obtained from Step 1) in 10 mL CH,Cl, was added 785 mg (3.77 mmol) PCl, and stirred for 1 Calc'd for C,H,N,O,S;: 595.2876. Found: 595.2874. To a solution of 1.12 g (1.88 mmol) of the 0.5M NH, in dioxane and stirred 16 hours. The

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Example 1406

(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1bensothiepin-5-yl]phenoxy]propyl]-4-asa-1asoniabicyclo[2,2,2]octane, methanesulfonate (salt)

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Step 1: Preparation of dimesylate intermediate

To a cooled (-20 °C) solution of 5.0 g (65.7 mmol) of 1,3-propanediol in 50 mL of triethylamine and 200 mL of methylene chloride was added 15.8 g (137.9 mmol) of methanesulfonyl chloride. The mixture was stirred for 30 minutes, then warmed to ambient temperature and partitioned between ethyl acetate and 1N HCl. The organic layer was washed with brine, dried over MgSO, and concentrated in vacuo to give 13.5 g (89%) of dimesylate intermediate as a clear yellowish oil: 'H NMR (CDCl,) & 2.12 (quintet, J = 4.5 Hz, 4H), 3.58 (8, 6H), 4.38 (t, J = 5.4 Hz)

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25 Step 2: Preparation of propyl mesylate intermediate

To a solution of 2.4 g (5.2 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenz-othiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 6.0 g (26.1 mmol) of dimesylate intermediate (obtained from Step 1) in 50 mL of acetone was added

0.95 (m, 6H), 1.06-1.52 (m, 10H), 1.57-1.70 (m, 1H), 3.6 g (26.1 mmol) of K₂CO₃. The reaction was heated 2.14-2.32 (m, 3H), 2.84 (s, 6H), 3.02 (s, 3H), 3.08 intermediate as a white foam: 'H NMR (CDCl,) & 0.86afforded 2.8 g (90%) of the propyl mesylate concentrated in vacuo. The residue was partitioned 6.65 (d, J = 8.7 Hz, 1H), 6.94(d, J = 8.6 Hz, 2H), 7.43 4.48 (t, J = 6.0 Hz, 2H), 5.49 (g, 1H), 6.11 (g, 1H), reflux overnight then cooled to ambient temperature and (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H). $(AB_q, J_{AB} = 15.0 \text{ Hz}, J = 46.9 \text{ Hz}, 4.09-4.18 (m, 3H),$ (Waters-Prep 500) using 36% ethyl acetate/hexanes in vacuo. Purification by silica gel chromatography washed with brine, dried over MgSO,, and concentrated between ethyl acetate and water. The organic layer was

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Step 3: Preparation of quaternary salt

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chloride/ethyl ether gave 1.3 g (91%) of the desired for C,,H,,N,O,S': 612.3835. Found: 612.3840. 8.9 Hz, 1H). MS (BS+) m/e 612.4. HRMS (BS+) Calc'd = 8.6 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 1H), 5.97 (8, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.90(d, J Hz, J = 42.2 Hz, 2H) 3.22-3.32 (m, 6H), 3.56-3.66 (m, 2H), 2.83 (8, 6H), 3.04 (8, 3H), 3.09 (AB_q , $J_{AB} = 15.6$ 1.57-1.70 (m, 1H), 2.12-2.25 (m, 3H), 2.28-2.39 (m, title compound as a white solid: mp. (dec) 230-235 °C; ambient temperature and concentrated in vacuo. was stirred at 60 °C for three hours, then cooled to of acetonitrile was added 0.3g (2.9 mmol) of 1,4mesylate intermediate (obtained from Step 2) in 20 ml 6H), 3.73-3.83 (m, 2H), 4.06-4.17 9m, 3H), 5.47 (s, Purification by trituration with methylene diazabicyclo[2.2.2]octane (DABCO). The reaction mixture ¹H NPAR (CDCl₃) & 0.86-0.95 (m, 6H), 1.04-1.52 (m, 10H), To a solution of 1.2 g (2.0 mmol) of propyl

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(polt) aseniabicyclo [2.2.2] octane, 4-methylbons ancoulfonate 2,3,4,5-totrahydro-4-hydroxy-1,1-dioxido-1bansothiapin-5-yl]phenoxy]propyl]-4-asa-1-(4R-cis)-1-[3-{4-[3,3-Dibutyl-7-(dimethylemine)-

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Step 1: Preparation of propyl tosylate intermediate A solution of 5-(4'-hydroxyphenyl)-7-

hours. The cream-colored slurry was cooled to 25 °C powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,3g, 10.9 mmol, obtained from Example 1402, Step 10) in NMR (CDCl,) 8 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.63 silica, 20-30% EtOAc/hexane) afforded the propyl and was filtered through a sintered glass funnel. The acetone (100 mL) at 25 °C under N, was treated with Purification by flash chromatography (4.4 x 35 cm concentrated in vacuo to provide a pale orange oil. aqueous NaCl (2 x 150 mL), and was dried (MgSO,) and saturated aqueous NaHCO $_1$ (2 x 150 mL) and saturated in EtOAc (150 mL). The organic layer was washed with filtrate was concentrated and the residue was dissolved and the resulting mixture was stirred at 65 °C for 21 propanediol di-p-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 tosylate intermediate (6.0 g, 80%) as a white foam: 'H

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(m, 1H), 2.14 (m, 2H), 2.21 (m, 1H), 2.41 (8, 3H), 2.81 (8, 6H), 3.06 (ABq, J = 15.1 Hz, J = 49.0 Hz, 2H), 4.01 (t, J = 5.3 Hz, 2H), 4.10 (m, 1H), 4.26 (t, J = 5.9 Hz, 2H), 5.29 (8, 1H), 5.48 (8, 1H), 5.98 (8, 1H), 6.51 (dd, J = 8.9, 1.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.9 Hz, 1H).

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Step 2: Preparation of quaternary salt

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8.3 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.9 2.4 Hz, 1H), 6.49 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (d, J of for 14 hours. The pale amber solution was cooled to 2.18 (m, 1H), 2.22 (m, 2H), 2.27 (8, 3H), 2.78 (8, 6H), acetonitrile (15 mL) at 25 °C under N, was treated with oil. The residue was dissolved in a minimal amount of - 8.5 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 5H), i.12-1.43 (br m, 9H), 1.61 (m, 1H), 1.65 (m, 1H), 3.07 (ABq, J = 15.1 Hz, J = 39.5 Hz, 2H), 3.49 (br 8, 1.5 eq.) and stirred at 50 °C for 6 hours, then at 25 compound (1.11 g, 90%) as a white amorphous solid: mp 4.09 (d, J = 7.3 Hz, 1H), 5.46 (B, 1H), 5.96 (d, J = Hz, 1H); HRMS. Calc'd for C18H, NO, S: 612.3835. Found: 6H), 3.68 (m, 1H), 3.74 (br s, 6H), 3.96 (br s, 2H), vigorously stirring for 4 hours, during which time a diazabicyclo[2.2.2]octane (DABCO, 0.26 g, 2.34 mmol, 15 °C and concentrated in vacuo to provide an amber 116.5-142 °C (decomposed); ¹H NMR (CDCl₁) & 0.89 (m, A solution of the propyl tosylate intermediate CH,Cl, (5 mL) and diluted with Et,O (100 mL) while collected (Et,O wash) to give the desired title white solid precipitated. The white solid was (1.05 g, 1.56 mmol, obtained from Step 1) in

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(4R-cis)-1-[4-[4-[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1benzothiepin-5-yl]phenoxy]butyl]-4-axa-1azoniabicyclo[2.2.2]octanemethanesulfonate (salt)

Step 1: Preparation of butyl mesylate intermediate

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J = 9.0 Hz, 2.7 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.42 resulting white foam was chromatographed through silica gel column, and eluted with 30% ethyl acetate/hexane to 10), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88 concentrated in vacuo and the crude was dissolved in 30 thispine-1,1-dioxide (obtained from Example 1402, Step give 1.02 g (77%) of butyl mesylate intermediate as a 2H), 5.49 (8, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.52 (dd, nh of ethyl acetate. The insoluble solid was filtered mmol) of potassium carbonate in 20 mL of acetone was white solid: ¹H NMR (CDCl₃) 8 0.90 (m, 6H), 1.20-1.67 2H), 4.11 (d, J = 6.90 Hz, 1H), 4.35 (t, J = 6.0 Hz, off and the filtrate was concentrated in vacuo. The (m, 12H), 1.98 (m, 4H), 2.22 (m, 1H), 2.83 (8, 6H), 3.04 (8, 3H), 3.08 (ABq, 2H), 4.05 (t, J = 5.55 Hz, hydroxyphenyl) -7- (dimethylamino) tetrahydrobenzo-(d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H). A mixture of 1.00 g (2.18 mmol) of 5-(4'stirred at reflux overnight. The mixture was

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Preparation of ester intermediate

= 7.1 Hz, 6H}, 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (s, 2.77 (s, 3H), 2.82 (s, 3H), 3.07 (ABq, 2H), 3.26 (t, J mp 248-251 °C; 'H NMR (CDCl₃) 8 0.91 (m, 6H), 1.14-1.47 was crushed and washed with ether. The solid was mmol) of DABCO in 10 mL of acetonitrile was stirred at 2.6 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.11H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.9 Hz, from methylene chloride and acetone as a white solid: the desired title compound which was recrystallized filtered off and dried in vacuo to give 540 mg (88%) of concentrated in vacuo to yield a white foam. The foam 80 °C for 4 hours. The reaction mixture was Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H). (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H), intermediate (obtained from Step 1) and 191 mg (1.71 A solution of 520 mg (0.85 mmol) of butyl mesylate

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exoniabioyelo[2.2.2] octano-4-mothylbonsenosulfonate benzothiopin-5-yl]phonomy]butyl]-4-ese-1-2,3,4,5-totrohydro-4-hydroxy-1,1-dioxido-1-(4R-cio)-1-{4-{4-{3,3-Dibutyl-7-(dimethylamino)-

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Step 1: Preparation of propyl tosylate intermediate

8.1 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.83 (m, 1H). J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz)5.96 (s, 1H), 6.46 (dd, J = 8.9, 1.4 Hz, 1H), 6.85 (d, propyl tosylate intermediate (6.0 g, 80%) as a white x 35 cm silica, 20-30% BtOAc/hexane) afforded the Hz, 2H), 3.93 (m, 2H), 4.06-4.13 (m, 4H), 5.44 (s, 1H), (8, 3H), 2.80 (8, 6H), 3.03 (ABQ, J = 15.1 Hz, J = 46.310H), 1.61 (m, 1H), 1.84 (m, 4H), 2.19 (m, 1H), 2.43 foam: 1H NMR (CDCl₃) & 0.89 (m, 6H), 1.10-1.44 (br m, orange oil. Purification by flash chromatography (4.4 aqueous NaCl (2 \times 150 mL). The extract was dried and filtered through a sintered glass funnel. The and the resulting solution was stirred at 65 °C for 21 butanediol di-p-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), powdered K₄CO, (3.8 g, 27.2 mmol, 2.5 eq.) and 1,4acetone (100 mL) at 25 °C under N, was treated with g, 10.9 mmol, obtained from Example 1402, Step 10) in (MgSO,) and concentrated in vacuo to provide a pale saturated aqueous NaHCO, (2 x 150 mL) and saturated in EtOAc (150 mL). The organic layer was washed with filtrate was concentrated and the residue was dissolved hours. The cream-colored slurry was cooled to 25 °C (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 A solution of 5-(4'-hydroxyphenyl)-7-

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Step 2: Preparation of quaternary salt

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dissolved in a minimal amount of CH2Cl2 (5.mL) and mL) at 25 °C under N2 was treated with diluted with $\mathtt{Et_2O}$ (100 mL) while vigorously stirring to provide an off-white solid. The residue was solution was cooled to 25 °C and concentrated in vacuo eq.) and stirred at 45 °C for 6 hours. The pale yellow diazabicyclo[2.2.2]octane (DABCO, 1.1 g, 10.1 mmol, 1.2 8.5 mmol, obtained from Step 1) in acetonitrile (100 A solution of propyl tosylate intermediate (5.8 g,

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Hz, J = 30.0 Hz, 2H), 3.05 (br s, 6H), 3.37 (br s, 6H), 3,H4,N,O,8,: C, 64.71, H, 7.96, N, 5.27. Found: C, 64.36; C, H, N, O, S: 626.3992. Found: 626.3994. Anal. Calc'd for 223-231 °C (decomposed); 1H NMR (CDC1,) 8 0.86 (m, 6H), 3.89 (m, 2H), 4.07 (d, J = 7.5 Hz, 1H), 5.39 (s, 2H), ..09-1.43 (br m, 12H), 1.61-1.90 (br m, 5H), 2.13 (m, IH), 2.25 (8, 3H), 2.75 (8, 6H), 3.03 (ABq, J = 15.1 recrystallized from EtOAc/hexane to give the desired title compound (5.7 g, 85%) as colorless needles: mp 5.97 (d, J = 1.6 Hz, 1H), 6.44 (dd, J = 8.9, 2.0 Hz, IH), 6.87 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.1 Hz, precipitated. The white solid was collected and 2H), 7.80 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for for 3 hours, during which time a white solid

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Example 1410

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(4R-cis) -4- [4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-4-hydroxy-1,1-dioxido-1-bensothiepin-5yl]phenoxy]-N,N,N-triethyl-1-butaneminium

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mesylate intermediate (obtained from Example 1408, Step 1) and 15 mL of triethylamine in 10 mL of acetonitrile evaporated and the residue was triturated with ether was heated at 50 °C for 2 days. The solvent was A solution of 1 g (1.64 mmol) of the butyl

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(d, J = 15 Hz, 1 H), 3.0 (d, J = 15 Hz, 1 H), 3.3 (m, 8 H), 4.0 (m, 4 H), 5.3 (s, 1 H), 5.9 (s, 1 H), 6.4 (m, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), and ethyl acetate to afford 500 mg (43%) of product as a semi-solid. $^{1}\mathrm{H}$ NWR (CDCl,) δ 0.8 (m, 6 H), 1-1.6 (m, 24 H), 2.1 (m, 1 H), 2.6 (B, 3 H), 2.7 (B, 6 H), 2.9 '.8 (d, J = 7 Hz, 1 H). MS m/e 615.

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benrothiepin-5-yl]phenoxy]butyl]-3-hydroxypyridinium, (4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1methanesulfonate (salt)

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mesylate intermediate (obtained from Example 1408, Step H), 2-2.4 (m, 3 H), 2.9 (8, 6 H), 3.1 (d, J = 15 Hz, 1 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J 1) and 234 mg (2.46 mmol) of 3-hydroxy pyridine in 1 mL 0.9 (m, 6 H), 1-1.5 (m, 10 H), 1.7 (m, 1 H), 1.9 (m, 2 of dimethylformamide was heated at 70 °C for 20 hours. H), 3.2 (d, J = 15 Hz, 1 H), 4.1 (m, 3 H), 4.7 (m, 2 triturated with ether and ethyl acetate to afford 990 mg (86%) of product as a semi-solid: 1H NMR (CDCl,) & A solution of 1 g (1.64 mmol) of the butyl the solvent was evaporated and the residue was

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= 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.7 (m, 1 H), 8.0 (m, 2 H), 8.2 (m, 1 H), 9.1 (e, 1 H). MS m/e 609.

Example 1412

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(4R-cis)-1-[5-[4-[3,3-Dibutyl-7-(dimethylomino)2,3,4,5-totrahydro-4-bydroxy-1,1-dioxido-1bonsothiepin-5-yl]phonoxy]pentyl]quinolinium,
mothonogulfonato (solt)

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Step 1: Preparation of pentyl mesylate intermediate

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To a stirred solution of 231 mg (5.79 mmol, 60% disp.) of NaH in 22 mL of DMP was added 2.05g (4.45 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino) tetra-hydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the mixture was added 18.02 g (55.63 mmol) of 1,5-diodopentane and the solution was stirred overnight at ambient temperature. DMP was removed by high vacuum and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO, and the concentrated residue was gurified by column chromatography to give the pentyl mesylate intermediate: 'H NMR (CDCl₃) & 0.90(q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6h), 3.0 (q, 2H), 3.22 (t, 2H), 3.95 (t, 2H), 4.1 (s,

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1H), 5.42 (a, 1H), 6.1 (d, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of quaternary salt

20 15 5 v 10.2 (d, 1H). HRMS. Calc'd for C, H, N,O,S: 657.3726. 7.42; N, 3.56; S, 8.41. 65.40; H, 7.50; N, 3.72; S, 8.52. Found: C, 62.9; H, Found: 657.3736. Anal. Calc'd for C,H,N,O,S.CH,O,S: C, 7.9 (t, 1H), 8.2 (t, 2H), 8.3 (q, 2H), 8.98 (d, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.4 (d, 2H), 7.82 (d, 1H), 4.1 (8, 1H), 5.28 (t, 2H), 5.42 (8, 1H), 5.95 (8, 1H), 2.25 (m, 18H), 2.8 (s, 9H), 3.0 (q, 2H), 3.95 (t, 2H), C18 column chromatography. The obtained material was chromatography to give the desired title compound as a The solution was heated at 45 °C under N, for 10 days. solid: mp 136 °C; 1H NMR (CDCl) 8 0.95(q, 6H), 1.05exchanged to its mesylate anion by ion exchange intermediate (obtained from Step 1) was added 3.94 g (30.5 mmol) of quinoline and 30 mL of acetonitrile. The concentrated residue was purified by reverse phase To 1.0g (1.53 mmol) of the pentyl mesylate

Example 1413

(48-cis) - [5-[4-[3,3-Dibutyl-7-(dimathylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-bensothiepin-5-yllphanoxylpantyl)propanedioic acid

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Step 1: Preparation of pentyl bromide intermediate

it ambient temperature for 1 hour. To the solution was 1402, Step 10), and the resulting solution was stirred was extracted with ethyl acetate and washed with brine. the extract was dried over MgSO,, and the concentrated added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and residue was purified by column chromatography to give temperature. DMF was removed in vacuo and the residue To a stirred solution of 0.63 g (15.72 mmol, 60% hydrobenzothiepine-1,1-dioxide (obtained from Example mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetradisp) of NaH in 85 mL of DMF was added 6.0 g (13.1 the mixture was stirred overnight at ambient

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Step 2: Preparation of dibenzyl ester intermediate

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7.4 (d, 2H), 7.9 (d, 1H).

0.84 g (2.952 mmol) of dibenzyl malonate (Aldrich), and (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 1H), 3.9 (t, thromatography to give the dibenzyl ester intermediate: To the mixture of 59 mg (1.476 mmol, 60% disp) of IH), 4.1 (d, 1H), 5.18 (s, 4H), 5.42 (s, 1H), 5.95 (s, NaH in 27 mL of THP and 9 mL of DMF at 0 °C was added H NMR (CDC1,) & 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 and the concentrated residue was purified by column vashed with brine. The extract was dried over MgSO, intermediate, and the mixture was stirred at 80 °C temperature for 15 min. To the solution was added residue was extracted with methylene chloride and overnight. Solvent was removed in vacuo, and the the resulting solution was stirred at ambient 0.5987 g (0.984 mmol) of the pentyl bromide

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1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 12H), 7.85 (d, 1H).

Step 3: Preparation of diacid

nours. The catalyst was filtered off, and the filtrate a solid: mp 118 °C; ¹H NMR (CDCl,) \$ 0.9 (d, 6H), 1.05umblent temperature under 20 psi of hydrogen gas for 2 was concentrated to give the desired title compound as dibenzyl ester intermediate (obtained from Step 2) and 3.95 (B, 2H), 4.1 (B, 1H), 5.42 (B, 1H), 5.95 (B, 1H), Anal. Calc'd for C,4H4NO,8: C, 64.63; H, 7.82; N, 2.22; 25 mg of 10% Pd/C in 30 mL of ethanol was agitated at HRMS. Calc'd for C,4H,NO,8: 632.3257. Found: 632.3264. 2.2 (m, 20H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.85 (d, 1H). S, 5.08. Found: C, 63.82; H, 7.89; N, 2.14; S, 4.93. A suspension of 0.539 g (0.664 mmol) of the

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Example 1414

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the pentyl bromide intermediate: 'H NMR (CDCl,) 8 0.90

(q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H),

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3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (g, 1H), 6.5 (d, 1H), 6.9 (d, 2H),

4R-cis) -3,3-Dibutyl-5-[4-[[5-

(diethylamino)pentyl]oxy]phenyl]-7-(dimethylamino)-1,3,4,5-tetrahydro-1-benrothiepin-4-ol 1,1-dioxide

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Step 1: Preparation of pentyl lodide intermediate

(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (3 g, 6.53 mmol, obtained from Example 1402, Step 10) in To a solution of 5-(4'-hydroxyphenyl)-7-

5 0.9 (m, 6 H), 1-1.5 (m, 11 H), 1.6 (m, 3 H), 1.8 (m, 7.9 (d, J = 7 Hz, 1 H). H), 4.1 (8, 1 H), 5.5 (8, 1 H), 6.1 (8, 1 H), 6.6 (m, 1 H), 3.2 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 4.0 (m, 1 4 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (d, J = 15 Hz, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), mmol) of the pentyl lodide intermediate: 'H NWR (CDCl) with hexane/ethyl acetate (1/5) to afford 2.92g (4.46 mmol) of 95% sodium hydride. The mixture was stirred magnesium sulfate and concentrated in vacuo. The organic layer was washed with brine, dried over was diluted in ethyl acetate and water. The aqueous 15 minutes at room temperature and dilodopentane was 100 mL of dimethylformamide was added 198 mg (7.83 residue was chromatographed over silica gel, eluting layer was extracted with ethyl acetate and the combined added. After one hour at room temperature the mixture

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Step 2: Preparation of amine

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6.00 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.2 Hz, 2.6 Hz, 6.3 Hz, 2H), 4.10 (d, J = 7.8 Hz, 1H), 5.48 (s, 1H), solid: 1H NMR (CDCl₃) & 0.89 (m, 6H), 1.20-1.47 (m, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.4 Hz, IH), 2.74-2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, J = 12H), 1.53-1.67 (m, 4H), 1.76-1.90 (m, 8H), 2.21 (m, magnesium sulfate and concentrated to yield 390 mg solution twice. The ethyl acetate layer was dried over 2H), 7.90 (d, J = 9.0 Hz, 1H). (85%) of the desired title compound as a yellow foamy washed with 50 mL of saturated sodium carbonate The foam was dissolved in 10 mL of ethyl acetate and concentrated in vacuo to yield a yellowish brown foam stirred at 100 °C overnight. The mixture was (3.81 mmol) of diethylamine in 3 mL of acetonitrile was iodide intermediate (obtained from Step 1) and 279 mg A solution of 550 mg (0.76 mmol) of the pentyl

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Example 1415

dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine (4R-c1a)-N-(Carboxymethyl)-N-[5-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-

Step 1: Preparation of diester intermediate

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structure; MS (M+H) m/e 717. removed in vacuo to give 9.6g (95%) of the diester extracted with methylene chloride. The volatiles was hours. The reaction mixture was diluted with water and mmol) of anhydrous Na,CO, was stirred at 160 °C for 3 intermediate (obtained from Example 1413, Step 1), 65 g (0.35 mol) of diethylaminodiacetate and 7.5 g (71 intermediate. 'H NMR spectrum was consistent with the A mixture of 8.6 g (14.1 mmol) of pentyl bromide

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Step 2: Preparation of diacid

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¹H NMR (CD,OD) 8 0.92 (t, 6H), 1.1-1.9 (m, 31H), 2.15 triturated with hexane, filtered to give 8.9g (93%) of and extracted with dichloromethane. The residue was hours. The reaction mixture was acidified with 1% HCl (m, 6H), 5.3(g, 1H), 6.1 (g, 1H), 6.6 (d, 1H), 7.0(d, (t, 1H),2.8(s, 6H), 3.15 (ABq, 2H), 3.75(m, 1H), 4.1 the desired title compound as a solid: mp 148-162 °C; mL) and water (50 mL) was stirred at 40 °C for 18 from Step 1) and 2.7g (64.3 mmol) of LiOH in THF (75 The mixture of the diester intermediate (obtained

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2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M+H) m/e 661. Anal. Calc'd for [C₁₁H₁N₂O₈S + 1.5H₂O]: C,61.11; H,8.06; N,4.07; S,4.66. Found: C,61.00; H,7.72; N,3.89; S,4.47.

Example 1416

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(4R-cis)-5-[4-[[5-[bis[2-

(Diethylamino) ethyljamino]pentyl]oxy/phenyl]-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-bensothlepin-4-ol 1,1-dioxide

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(m, 2 H), 4.0 (m, 1 H), 4.1 (8, 1 H), 5.4 (8, 1 H), 6.0 2.9 (d, J = 15 Hz, 1 H), 3.1 (d, J = 15 Hz, 1 H), 3.9 oil. ¹H NMR (CDCl₃) 8 0.8 (m, 6 H), 1-1.6 (m, 28 H), 1.8 reverse phase chromatography. The fractions containing A solution of 1 g of pentyl iodide intermediate N, N, N', N' -tetraethyl diethylenetriamine was heated to residue was dried and concentrated in vacuo to afford 840 mg (74%) of the desired title compound as a thick (8, 1 H), 6.4 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 80 °C for 4 hours. The mixture was dissolved in ethyl (m, 2 H), 2.1 (m, 1 H), 2.5 (m, 18 H), 2.7 (s, 6 H), washed with brine, dried over magnesium sulfate, and the product were concentrated in vacuo, dissolved in (1.53 mmol, obtained from Example 1414, Step 1) in acetate and saturated NaHCO,. The organic layer was sthyl acetate and washed with saturated NaHCO,. The concentrated in vacuo. The residue was purified by

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(d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS (M+H) m/e 743.

Example 1417

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(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-5-[4-[[5-[[3-(iH-imidaxol-4yl)ethyl]amino]pentyl]oxy]phenyl]-1-benxothiepin-4-ol

1,1-dioxide

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A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) and 3.4 g (30.6 mmol) of histamine was heated to 50 °C for 17 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with ether to afford 588 mg (60%) of the desired title compound as a semi-solid: "H NMR (CDCl,) & 0.9 (m, 6 H), 1-1.7 (m, 14 H), 1.9 (m, 3 H), 2.0 (m, 2 H), 4.0 (m, 2 H), 2.8 (a, 6 H), 3.0 (m, 3 H), 5.5 (m, 1 H), 6.5 (m, 1 H), 6.8 (s, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (m, 3 H), 7.9 (d, J

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. 8 Hz, 1 H). MS (M+H) m/e 639.

(4R-cis) -N-(5-[4-[3,3-Dibutyl-7-(dimethylomino)2,3,4,5-totrahydro-4-hydroxy-1,1-dioxido-1benrothiopin-5-yl]phenoxy]pentyl]-N'-othyl-N,N',N'totromothyl-1,2-ethanodiominium dichlorido

Step 1: Preparation of pentyl bromide intermediate

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(t, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 5.99 (d, 1H), 6.50 10) and sodium hydride (0.250g, 6.25 mmol) in 30 mL of as a white foamy solid (1.783g, 80%): 'H NWR (CDCL,) & IH), 2.80 (8, 6H), 3.05 (ABg, 2H), 3.42 (t, 2H), 3.98 evaporation in vacuo gave pentyl bromide intermediate through silica gel eluting with 20% EtOAc/hexane and (1.680g, 3.66 mmol, obtained from Example 1402, Step mixture was extracted with BtOAc (3x50 mL). Organic dibromopentane (6.0 mL/44.0 mmol), and the resulting 0.84-0.95 (m, 6H), 1.02-1.56 (m, 10H), 1.58-1.70 (m, diluted with brine (100 mL) and H,O (20 mL), and the mixture was stirred for 18 hours. The reaction was 3H), 1.78-2.03 (m, 4H), 2.15-2.24 (m, 1H), 2.77 (s, (dd, 1H), 6.91 (d, 2H), 7.40 (d, 2H), 7.88 (d, 1H). (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide DMP was stirred in a dry 100 mL round-bottom flask concentrated in vacuo. Purification by filtration layers were combined, dried (MgSO,), filtered and A mixture of 5-(4'-hydroxyphenyl)-7under N. To this solution was added 1,5-

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Step 2: Preparation of mono-quaternary salt

3.18 (m, 1H), 2.20 (s, 6H), 2.67 (t, 2H), 2.74 (s, 6H), 3.75 (m, 4H), 3.90 (t, 2H), 4.01 (8, 1H), 5.37 (8, 1H), with ethyl ether. The solvent was decanted to yield a tetramethylethylenediamine (1.0 mL/6.62 mmol) in 30 mL of acetonitrile was stirred at 40.°C for 12 hours, and the reaction mixture was concentrated in vacuo to give wice, and the resulting sticky solid was concentrated 2.98 (ABq, 2H), 3.30-3.42 (m, 1H), 3.38 (s, 6H), 3.60was dissolved in acetonitrile (1.5 mL) and triturated (t, 6H), 0.96-1.64 (m, 13H), 1.62-1.85 (m, 4H), 2.03an off-white foamy solid (1.052g). The crude product white foamy solid (0.951g, 94%): 1H NMR (CDC1,) & 0.81 (0.853g, 1.40 mmol, obtained from Step 1), N,N,N',N'n vacuo to give the mono-quaternary salt as an offsticky solid. This trituration method was repeated 5.92 (8, 1H), 6.41 (dd, 1H), 6.81 (d, 2H), 7.32 (d, The mixture of pentyl bromide intermediate 2H), 7.77 (d, 1H).

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Step 3: Preparation of di-quaternary salt

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The mono-quaternary salt (0.933g, 1.29 mmol, obtained from Step 2), iodoethane (0.300 mL/3.75 mmol), and acetonitrile (30.0 mL) were combined in a 4 oz. Flacher Porter bottle. The reaction vessel was purged with Ns, sealed, equipped with magnetic stirrer, and heated to 50 °C. After 24 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give a yellow foamy solid (1.166g). The solid was dissolved in methylene chloride/acetonitrile and precipitated with ethyl ether. After cooling to 0 °C overnight, the resulting solid was filtered, washed with ethyl ether and concentrated in vacuo to yield the di-quaternary salt as an off-white solid (1.046g, 92%): ¹H NMR (CD,OD) & 0.59 (t, 6H), 0.70-1.10 (m, 9H), 1.16

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H). 3.78 (m, 4H), 3.80 (s, 4H), 4.93 (s, 1H), 5.71 (s, 1H), 2.98 (s, 6H), 3.02 (s, 6H), 3.22-3.37 (m, 4H), 3.63-6.22 (dd, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.40 (d, (t, 3H), 1.22-1.80 (m, 9H), 2.42 (s, 6H), 2.78 (d, 2H),

Step 4: Preparation of quaternary di-chloride salt

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1H), 6.61 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 4H), 5.02 (8, 1H), 5.72 (8, 1H), 6.19 (d, J = 8.4 Hz, 3.24-3.50 (m, 4H), 3.68 (8, 2H), 3.81 (8, 2H), 4.16 (8, H₂O/acetonitrile to give the desired title compound as Biorad AG 2X8 resin and eluting with 70% C,,He,N,O,SC1: 708.4541. Found: 708.4598. 2H), 7.46 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for (s, 6H), 2.78 (s, 2H), 3.08 (s, 6H), 3.11 (s, 6H), 9H), 1.16 (t, J = 6.6 Hz, 3H), 1.24-1.90 (m, 9H), 2.50 ¹H NMR (CD₃OD) δ 0.59 (t, J = 6.0 Hz, 6H), 0.70-1.12 (m. a white foamy solid (0.746g, 84%); mp 193.0-197.0 °C; converted to its corresponding dichloride salt using The iodobromosalt (obtained from Step 3) was

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tetramethyl-1,6-hexanediaminium dichloride dioxido-1-benrothiepin-5-yl]phenoxy]pentyl]-N,N,N'N' [4R-[4a,5a(4R*,.5R*)]]-N,N'-bis[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3;4,5-tetrahydro-4-hydroxy-1,1-

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10 25 20 15 35 ä ហ N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100g, 0.580 4H), 4.08 (br s, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.51 mmol, obtained from Example 1418, Step 1) and as a white foamy solid (0.676g, 86%); mp 178.0-182.0 12H), 3.52 (br s, 6H), 3.72 (br s, 4H), 3.97 (br s, 12.3 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.35 (s, 1.01-1.70 (m, 30H), 1.76-2.08 (m, 12H), 2.18 (t, J =with ethyl ether. After cooling to 0 °C, the solvent with N_2 , sealed, equipped with magnetic stirrer and Fischer Porter bottle. The reaction vessel was purged mmol) in 5 mL of acetonitrile were placed in a 4 oz. 30H), 1.75-2.06 (m, 12H), 2.16 (t, J = 12.9 Hz, 2H), with 70% H,O/CH,CN to give the desired title compound J = 7.8 Hz, 4H), 7.83 (d, J = 8.7 Hz, 2H). The desired dibromide salt as an off-white foamy solid sticky solid was concentrated in vacuo to give the solid was dissolved in acetonitrile and precipitated vacuo to give an off-white foamy solid (1.141g). The heated to 50 °C. 614.4118. Found: 614.4148. 6.87 (d, J = 8.4 Hz, 4H), 7.38 (d, J = 8.1 Hz, 4H), 6.49 (d, J = 9.0 Hz, 1H), 6.50 (d, J = 9.0 Hz, 1H), (s, 2H), 5.42 (s, 2H), 5.986 (s, 1H), 5.993 (s, 1H), s, 6H), 3.70 (br s, 4H), 3.96 (t, J = 5.4 Hz, 4H), 4.08 2.79 (8, 12H), 3.03 (ABQ, 4H), 3.33 (8, 12H), 3.49 (br °C; 'H NMR (CDCl₁) & 0.80-0.90 (m, 12H), 1.01-1.70 (m, dichloride salt using Biorad AG 2X8 resin and eluting dibromide salt was converted to its corresponding (d, J = 9.0 Hz, 2H), 6.86 (d, J = 7.8 Hz, 4H), 7.38 (d, J = 7.8 Hz, 4H)(0.843g, quantitative): 'H NMR (CDCl₃) 8 0.85 (m, 12H), trituration method was repeated, and the resulting was decanted to yield a sticky off-white solid. This was cooled to ambient temperature and concentrated in 7.84 (d, J = 8.7 Hz, 2 H). HRMS. Calc'd for $C_{16}H_{16}N_{1}O_{4}S$ The pentyl bromide intermediate (1.002g, 1.64 After 15 hours, the reaction mixture

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(4R-cis)-3,3-Dibutyl-7-(dimsthylamino)-2,3,4,5tetrahydro-5-[4-[[5-(lH-totrasol-5yl)pentyl]oxy]phanyl]-1-bonsothiopin-4-ol 1,1-dioxido

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Step 1: Preparation of pentyl bromide intermediate

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(85%) of the pentyl bromide intermediate as a colorless ..04-1.52 (m, 10H), 1.58-1.65 (m, 3H), 1.82 (p, J = 6.8 (t, J = 6.7 Hz, 2H), 3:99 (t, J = 6.3 Hz, 2H), 4.10 (s, To a stirred suspension of 1.01 g (25.4 umol, 60% oil dispersion) of sodium hydride in 150 mL of DMF was dibromopropane was added. The reaction was stirred at umbient temperature for 1.5 hours and quenched with 50 Purification by silica gel chromatography (Waters-Prep toam: mp 65-70 °C; ¹H NWR (CDC1,) 8 0.84-0.98 (М, 6H), 2.82 (s, 6H), 3.06 (ABq, Ja = 15.2, 45.3 Hz, 2H), 3.44 500) using 25% ethyl acetate/hexanes afforded 10.17 g nd of saturated NH,Cl. The reaction was diluted with Hz, 2H), 1.94 (p, J = 7.0 Hz, 2H), 2.12-2.26 (m, 1H), (H), 5.47 (8, 1H), 6.15 (d, J = 2.7 Hz, 1H), 6.68 (dd, sthyl acetate, washed with water, brine, dried over After 30 minutes the reaction was cooled in a water dimethylamino)tetrahydrobenzothiepine-1,1-dioxide obtained from Example 1402, Step 10) in portions. added 9.0g (19.5 mmol) of 5-(4'-hydroxyphenyl)-7bath (15 °C) and 4.48 g (195 mmol) of 1,5-1950, filtered and concentrated in vacuo.

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J=2.5, 8.4 Hz, 1H), 6.91 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.93 (d, J=8.7 Hz, 1H).

Step 2: Preparation of pentyl nitrile intermediate

In 1 mL of DMSO was added 37 mg (0.745 mmol) of sodium 19H), 1.58-1.92 (m, 7H), 2.16-2.28 (m, 1H), 2.41 (t, J Hz, lH), 6.92 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, the pentyl bromide intermediate (obtained from Step 1) organic layer was washed with brine, dried over MgSO, e 6.9 Hz, 2H), 2.83 (в, 6H), 3.08 (ABq, 15.0, 47.5 Hz, 1H), 6.07 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 2.4, 8.7 (H), 7.92 (d, J = 8.7 Hz, 1H). MS (ES, M+H) m/e 555. To a stirred solution of 378 mg (0.621 mmol) of filtered, and concentrated in vacuo to afford 278 mg 2 H), 4.01 (t, J=6.2 Hz, 2 H), 4.1 (8, 1 H), 5.49 (8, concentrated under a nitrogen stream and the residue 0.86-0.96 (m, 6H), 1.02-1.21(m, 1H), 1.21-1.52 (m, intermediate as a colorless foam: 'H NMR (CDC1,) & (93% RPHPLC purity, ca. 75%) of the pentyl nitrile partitioned between ethyl acetate and water. cyanide. The reaction was stirred at ambient temperature for 16 hours. The reaction was

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Step 3: Preparation of tetrazole

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A solution of 275 mg (0.5 mmol) of the nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene was stirred with heating at 80 °C for 60 hours. The reaction was concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 226 mg of the desired title compound (75%) as a colorless foam: mp 80-85 °C; "H NMR (CDC1,) & 0.83-0.95 (m, 6H), 1.30-1.52 (m, 10H), 1.52-1.73 (m, 3H), 1.79-1.99 (m, 4H), 2.14-2.26 (m, 1H), 2.91 (s, 6H), 5.47 (s, 1H),

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6.28 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 2.7, 8.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 8.7 Hz, 1H). HRMS Calc'd for C₃₂H₄₈N₄O₄S: 598.3427. Found: 598.3443.

Example 1421

(4R-cis)-4-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-11bensothiepin-5-yl]phenoxy]pentyl]oxy]-2,6pyridinecarboxylic acid

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25 20 15 g (163.75 mmol) of 1,5-dibromopentane, and stirred Step 1: Preparation of pentyl bromide intermediate and washed with brine. The extract was dried over overnight at ambient temperature. DMF was removed in temperature for 1 hour. To the solution was added 37.7 10), and the resulting solution was stirred at ambient (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 intermediate: 'H NMR (CDCl₃) & 0.90 (q, 6H), 1.05-2.0 column chromatography to give the pentyl bromide MgSO, and the concentrated residue was purified by vacuo and the residue was extracted with ethyl acetate thiepine-1,1-dioxide (obtained from Example 1402, Step hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-NaH in 85 mL of DMF was add 6.0g (13.1 mmol) of 5-(4'-To a solution of 0.63 g (15.72 mmol, 60% disp) of

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(t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Esterification of chelidamic acid

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A solution of 10 g (54.6 mmol) of chelidamic acid, 23.0 g (120.12 mmol) of 1-(3-dimethyl amino propyl)-3 ethyl carbodiimide hydrochloride, 1.33 g (10.8 mmol) of 4-dimethyl amino pyridine, and 12.4 mL (120.12 mmol) of benzyl alcohol in 100 mL of DMF was stirred at ambient temperature overnight under N₁. DMF was removed in vacuo and the residue was extracted with methylene chloride, washed with 5% NaHCO₁, 5% acetic acid, H₂O₂, and brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give dibenzyl chelidamic ester: 'H NMRR (CDC1₂) & 5.4 (s, 4H), 7.4 (m, 12H).

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Step 3: Preparation of pyridinyl benzyl ester

intermediate

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chromatography to give the pyridinyl dibenzyl ester concentrated residue was purified by column overnight at 40 °C. DMF was removed in vacuo, and the added 1.0 g (1.643 mmol) of the pentyl bromide (8, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3-7.5 (m, 12H) intermediate: 'H NMR (CDCl,) & 0.90 (q, 6H), 1.05-2.0 with brine. The extract was dried over Mg8O,, and the residue was extracted with ethyl acetate and washed ambient temperature for 1 hour. To the solution was 7.78 (s, 2H), 7.9 (d, 1H). (t, 2H), 4.1 (s, 1H), 5.4 (s, 4H), 5.42 (s, 1H), 6.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.0 intermediate and the mixture was stirred under $N_{
m z}$ (obtained from Step 2) in 17.5 mL of DMF was stirred at and 0.716g (1.972 mmol) of dibenzyl chelidamic ester A solution of 79 mg (1.972 mmol, 60% disp) of NaH

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Step 4: Preparation of pyridinyl diacid

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A suspension of 0.8813 g (0.99 mmole) of dibenzyl ester (obtained from Step 3) and 40 mg of 10% Pd/C in 35 mL of ethanol and 5 mL of THP was agitated at amblent temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 143 °C; 1H NPR (THP-d8) 0.95 (q, 6H), 1.05-1.65 (m, 15H), 1.9 (m, 4H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 4.1 (s, 3H), 4.3 (s, 2H), 5.4 (d, 2H), 7.78 (d, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.78 (d, 1H), 7.82 (s, 2H). HRWS. Calc'd for C₁,H₆M₃O₅S: C, 64.20, H, 7.09; N, 3.94; S, 4.51. Found: C, 62.34; H, 6.97; N, 4.01; S, 4.48.

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tample 1422

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(4R-cis) - [5- [4- [3,3-bibutyl-7- (dimothylomino) -2,3,4,5totrohydro-4-hydroxy-1,1-dioxido-1-bensothiopin-5yl]phonoxy]pentyl]guanidino

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Step 1: Preparation of pentyl azide intermediate

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To a stirred solution of 200 mg (0.328 mmol) of the pentyl bromide intermediate (obtained from Example 1420, Step 1) in 0.75 mL of DMSO was added 32 mg (0.493

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(t, J = 6.3 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 4.09 (s, used without further purification: mp 45-50 °C, 'H NMR mmol) of sodium azide and a catalytic amount of sodium 2.81 (8, 6H), 3.06 (ABq, Ja = 15.0, 48.0 Hz, 2H), 3.31 1H), 5.47 (8, 1H), 6.10 (d, J = 1.8 Hz, 1H), 6.63 (dd, CDCl₃) 8 0.83-0 93 (m, 6H), 1.03-1.48 (m, 10H), 1.54organic layer was washed with brine, dried over MgSO,, J = 2.7, 9.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.39 concentrated under a nitrogen stream and the residue filtered, and concentrated in vacuo to afford 155 mg 1.74 (m, SH), 1.78-1.86 (m, 1H), 2.14-2.26 (m, 1H), azide intermediate as a colorless foam. Sample was (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H). MS (92% RPHFLC purity, about 76% yield) of the pentyl partitioned between ethyl acetate and water. iodide. The reaction was stirred at ambient temperature for 64 hours. The reaction was FAB, M+H) m/e 571.

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Step 2: Preparation of pentyl amine intermediate

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To a solution of 0.67 g (1.17 mmol) of the azide intermediate (obtained from Step 1) in 75 mL of ethanol was added 0.10 g of 10¢ palladium on carbon and the mixture shaken under 49 psi of hydrogen at ambient temperature for 3.5 hours. The reaction was filtered through cellte and concentrated in vacuo to give 0.62 g (86¢ RPHPLC purity, ca. 84¢) of pentyl amine intermediate as an off-white foam. The sample was used without further purification: mp 70-85 °C; ¹H NMR (CDC1), 6 0.86-0.96 (m, 6H), 1.06-1.75 (m, 15H), 1.79-1.93 (m, 4H), 2.15-2.28 (m, 1H), 2.82 (s, 6H), 2.96-3.20 (m, 4H), 3.99 (t, J = 6.0 Hz, 2H), 4.04-4.14 (m, 1H), 5.49 (s, 1H), 6.00 (d, J = 1.5 Hz, 1H), 6.51 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). MS (ES, M+H)

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Step 3: Preparation of guanidine

8.1 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.89 (d, J = 8.7s, 2H), 4.12 (s, 1H), 5.46 (s, 1H), 6.01 (d, J = 2.12.24 (m, 1H), 2.81 (s, 6H), 2.99-3.19 (m; 4H), 3.98 (br mg (43%) of the desired title compound as colorless Delta prep) using 60% water/acetonitrile afforded 120 Purification by reversed phase chromatography (Watersmmol) of diisopropylethylamine. The reaction was hydrochloride in 1.5 mL of DMF was added 71 mg (0.551 mg (0.551 mmol) of 1H-pyrazole-1-carboxamidine pentyl amino intermediate (obtained from Step 2) and 81 Hz, 1H). HRMS. Calc'd for C11H6N,0,S:586.3552 Hz, 1H), 6.51 (dd, J = 2.1, 8.0 Hz, 1H), 6.92 (d, J =stirred at ambient temperature for 16 hours. (m, 6H), 1.05-1.17 (m, 1H), 1.26-1.90 (m, 16H), 2.07foamy solid: mp 67.0-72.5 °C; 1H MMR (CDCl₃) & 0.89-0.93 Found (M+H): 587.3620 To a stirred solution of 258 mg (0.474 mmol) of

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Example 1423

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2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1bensothiepin-5-yl]phenoxy]pentyl]glycine (4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-

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Step 1: Preparation of pentyl azide intermediate

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mg, 0.657 mmol, obtained from Example 1420, Step 1) in To a solution of pentyl bromide intermediate (400

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4H), 7.91 (d, J = 7.8 Hz, 1H). J = 7.58 Hz, 1H), 6.68 (d, <math>J = 7.7 Hz, 1H), 7.14 (ABq)= 7.7 Hz, 2H), 4.91 (br s, 1H), 5.47 (s, 1H), 6.13 (d, 6H), 3.08 (q, 2H), 3.44 (t, J = 7.7 Hz, 2H), 3.99 (t, J 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.82 (s, 0.90 (m, 7H), 1.05-1.56 (m, 12H), 1.59-1.71 (m, 3H), intermediate as a yellow oil: H NMR (CDCl₃) 8 0.82vacuo to give 390 mg (quantitative) of pentyl azide The organic layer was dried (MgSO4) and concentrated in washed with water (2x 100 mL) and brine (1x 100 mL). solution was diluted with 100 mL ethyl acetate, then solution was stirred at 23 °C for 16h. The reaction mg, 0.723 mmol, 1.1 eq), and the resulting clear dimethyl sulfoxide (20 mL) was added sodium azide (47

Step 2: Preparation of amino ester intermediate

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g, 1.54 mmol, 2.25 eq) and bromo acetic acid benzyl mL), followed by the addition of triethylamine (0.156 celite and concentrated in vacuo to give a yellow oil. 0.684 mmol, obtained from Step 1) and 100 mg of 1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J= 8.3 Hz, and brine (1x 20 mL). The organic layer was dried ethyl acetate (20 mL) and washed with water (2x 20 mL) concentrated in vacuo, and the residue was dissolved in under an atmosphere of hydrogen gas (48 psi) for 4.5 palladium on carbon in ethanol (15 mL) was agitated 1H), 2.75 (d, J = 7.83 Hz, 1H), 2.795 (s, 6H), 3.08 (q, amino ester intermediate as a yellow oil: 'H NMR (MgSO,) and dried in vacuo to give 420 mg (89%) of the stirred at 23 °C for 48 hours. The reaction was ester (0.212 g, 0.925 mmol, 1.35 eq). The reaction was hours. The ethanolic suspension was filtered through 2H), 3.68-3.85 (m, 2H), 3.87-4.04 (m, 2H), 4.09 (s, (CDCl₁) 8 0.82-0.90 (m, 6H), 1.05-1.56 (m, 14H), 1.58-The oil was immediately diluted with acetonitrile (15 A suspension of pentyl azide intermediate (390 mg

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1H), 5.147 (8, 1H), 5.46 (8, 1H), 5.98 (d, J = 7.58, 1H), 6.50 (dd, 1H), 6.85-6.87 (m, 2H), 7.28-7.45 (m, 5H), 7.89 (d, J = 8.0 Hz, 1H). MS (ES) m/e 693.

Step 3: Preparation of acid

A suspension of benzyl ester intermediate (0.420g, 0.61 mmol, obtained from Step 2) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 16h. The suspension was filtered through celite, and concentrated in vacuo to give 0.130g of a yellow semisalid. The material was triturated with diethyl ether and the remaining semi-solid was dried in vacuo to give 0.19 g (52%) of the desired title compound as a yellow semi solid: "H NMR (CDC1,) & 0.86 (br s, 7H), 1.0-1.72 (m, 18H), 1.79 (br s, 2H), 1.98 (s, 2H), 2.09-2.24 (m, 2H), 2.78 (s, 6H), 2.99 (q, 2H), 3.96 (bs, 2H), 4.08 (s, 1H), 5.46 (s, 1H), 5.97 (s, 1H), 6.40-6.49 (m, 1H), 7.14 (ABG, 4H), 7.85 (t, J = 7.93 Hz, 1H). MS (ES) m/e 603.

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Example 1424

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(4R-cis) -4-[[4-[3,3-Dibutyl-7-(dimethylumino) -2,3,4,5tetrahydro-4-hydrexy-1,1-diexide-1-benrethiopin-5yl]phenexy]methyl]benreic acid

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Step 1: Preparation of benzoate intermediate

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mmol) of 95% sodium hydride and stirred for 10 minutes. Intermediate: $^1 \! H$ NMR (CDCl₃) δ 0.86-0.96 (m, 6H), 1.14-15.1 Hz, 1H), 3.92 (8, 3H), 4.09-4.15 (m, 1H), 5.17 (8, (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.93 (d, extracted with ethyl acetate, washed with brine, dried thiepine-1,1-dioxide (obtained from Example 1402, Step 2H), 5.49 (8, 1H), 5.94 (d, J = 2.2 Hz, 1H), 6.50 (dd, 2.80 (8, 6H), 2.99 (d, J = 15.1 Hz, 1H), 3.15 (t, J = 10) in 10 mL dimethylformamide was added 35 mg (1.39 To the reaction mixture was added 525 mg (2.29 mmol) J = 8.9, 2.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.43 1.47 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.23 (m, 1H), To a solution of 0.53 g (1.15 mmol) of 5-(4'evaporated to afford 0.51 g (73%) of the benzoate methyl 4-(bromomethyl)benzoate and stirred for 16 over magnesium sulfate, filtered and the solvent hydroxyphenyl) -7- (dimethylamino) tetrahydrobenzohours. Water was added to the reaction mixture, J = 8.9 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H).

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Step 2: Preparation of acid

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A solution of 0.51 g (0.84 mmol) of the benzoate intermediate (obtained from Step 1) and 325 mg (3.53 mmol) of KOS1(CH₃), (Aldrich) in 16 mL THP was stirred for 3.5 hours. The THP was evaporated, water added, extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.30 g (60%) of the desired title compound as a white solid: mp 156 - 159 °C; 'H NWR (CDCl₃) & 0.89-0.94 (m, 6H), 1.24-1.43 (m, 10H), 1.62-1.66 (m, 1H), 2.20-2.24 (m, 1H), 2.84 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (d, J = 15.1 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.57 (d,

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J = 8.3 Hz, 2H, 7.95 (d, J = 8.9 Hz, 1H), 8.13 (d, J = 8.9 Hz)8.1 Hz, 2H). HRMS. Calc'd for C, H, NO, S: 594.2889 Found: 594.2913.

2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1pyridinium chloride bensothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-

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Step 1: Preparation of chlorobenzyl intermediate

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concentrated in vacuo to provide a yellow oil EtOAc (2 x 150 mL) and the combined organic extracts (2 x 150 mL). The aqueous layer was extracted with concentrated to 1/5 of original volume. The residue dichloro-p-xylene (6.7 g, 38.1 mmol, 3.5 eq.) and the g, 10.9 mmol, obtained from Example 1402, Step 10) in The combined extracts were dried (MgSO4) and were washed with saturated aqueous NaCl (2 x 150 mL was dissolved in EtOAc (150 mL) and washed with water The reaction mixture was cooled to 25 °C and resulting solution was stirred at 65 °C for 48 hours. powdered K₂CO₃ (2.3 g, 16.3 mmol, 1.5 eq.) and α,α' acetone (100 mL) at 25 °C under N, was treated with (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 A solution of 5-(4'-hydroxyphenyl)-7-

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1.63 (m, 1H), 2.22 (m, 1H), 2.81 (s, 6H), 3.05 (ABq, J intermediate (4.7 g, 72%) as a white foam: ¹H NWR = 8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, J = 8.9 Hz, 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.6 Hz, 1H), 7.00 (d, J4.60 (8, 2H), 5.11 (8, 2H), 5.48 (8, 1H), 5.96 (d, J a silica, 25-40% EtOAc/hexane) afforded the chlorobenzyl Purification by flash chromatography (5.4 x 45 cm = 15.1 Hz, \mathcal{J} = 50.0 Hz, 2H), 4.11 (d, \mathcal{J} = 8.1 Hz, 1H), (CDCl₃) 8 0.89-0.94 (m, 6H), 1.12-1.48 (br m, 10H),

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Step 2: Preparation of quaternary salt

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4.09 (s, 1H), 5.00 (s, 2H), 5.38 (s, 1H), 5.91 (d, J= g, 1.7 mmol, obtained from Step 1) in acetonitrile (5 Hz, 1H), 8.58 (br s, 1H), 9.69 (d, J = 5.8 Hz, 2H), 8.9 Hz, 2H), 7.93 (t, J = 6.8 Hz, 1H), 8.34 (t, J = 7.72.4 Hz, 1H), 6.26 (B, 2H), 6.41 (dd, J = 8.9, 2.4 Hz, 6H), 1.06-1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H) yellow solid: mp 154-156 °C; H NMR (CDCl) 8 0.83 (m, to give the desired title compound (1.08 g, 96%) as a = 7.7 Hz, 4H), 7.73 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, J 2.71 (s, 6H), 3.02 (ABq, J = 15.1 Hz, J = 28.4 Hz, 2H) solution was cooled to 25 °C and concentrated in vacuo mL) at 25 °C under N_2 was treated with pyridine (5 mL) HRMS. Calc'd for $C_{3p}H_{4p}N_{2}O_{4}S$; 641.3413. Found; 641.3425. and stirred at 35 °C for 36 hours. The pale amber A solution of the chlorobenzyl intermediate (1.0

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Example 1426

(4R-cis).1-[[4-[14-[3,3-Dibuty]-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1bensothispin-5-yl]phenoxy]methyl]phenyl]methyl]-4-asa1-asoniabicyclo[2,2,2]octane chloride

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similar to the one outlined in Example 1425, Step 1) in precipitate was formed. The slurry was stirred at 35°C (8, 6H), 3.06 (ABq, J = 15.1 Hz, J = 43.3 Hz, 2H), 3.16 (8, 2H), 5.14 (8, 2H), 5.48 (8, 1H), 5.96 (8, 1H), 6.49 washed with 1 L of acetonitrile to give 9.6 g (93%) the 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.26 (m, 50 mL of acetonitrile was added dropwise over a 30 min acetonitrile at 35° C, during the addition, a colorless (8, 6H), 3.76 (8, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09 for an additional 2 h. The product was collected and 123-230°C (decomposed); H NMR (CDC1,) 8 0.89 (m, 6H), Under N3, a solution of 8.7 g (14.5 nmol) of the chlorobenzyl intermediate (obtained from a procedure title compound as a colorless crystalline solid: mp diazabicyclo[2.2.2]octane (DABCO) in 40 mL of period to a solution of 2.9 g (26.2 mmol) of

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1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H), HRMS. Calc'd for C₄₀H₄N₃O₅S: 674.3992. Pound: 674.4005.

xample 1426

(4R-cis)-1-[[4-[[4-[3,3-Dibuty]-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1bensothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-ese1-ssoniabicyclo[2,2,2]octane chloride

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A solution of the chlorobenzyl intermediate (4.6 g, 7.7 mmol, obtained from Example 1425, Step 1) in acetonitrile (100 mL) at 25°C under N, was treated with diazabicyclo[2.2.2]-octane (DABCO, 0.95 g, 8.5 mmol, 1.1 eq.) and attrred at 35°C for 2 hours, during which time a white solid precipitated out. The white solid was collected, washed with CH,CN and recrystallized from CH,OH/Et,O to give the title compound (4.95 g, 91%) as a white solid: mp 223-230°C (decomposed); "H NWR (CDCl,) & 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABG, J = 15.1 Hz, J = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, J = 8.9 Hz, 1H),

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6.99 (d, J = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for $C_{40}H_{82}N_{3}O_{4}S$: 674.3992. Found: 674.4005.

Example 1427

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4R-cis)-N-(Carboxymethyl)-N-[[4-[3-3-dtbutyl-7-(dimethylemino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-bensothiepin-5-yl]phenoxy]methyl]phenyl]methyl]glycine

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Step 1: Preparation of chlorobenzyl intermediate

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To a stirred solution of 144 mg (3.59 mmol, 60% disp) of NaH in 29 mL of DMF was added 1.5 g (3.26 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-hydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 45 min. To the solution was added 7.13 g (40.75 mmol) of dichloro p-xylene, and the mixture was stirred overnight. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO, and the concentrated residue was purified by column chromatography to give the chlorobenzyl intermediate: 'H NMR (CDC1,) & 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.1

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(d, 1H), 4.6 (s, 2H), 5.1 (s,2H), 5.5 (s, 1H), 6.0 (s, 1H), 6.6 (d,1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.8 (d,1H)

Step 2: Preparation of amino diester

A mixture of 1.03 g (1.72 mmol) of chlorobenzyl intermediate (obtained from Step 1), 1.63 g (8.6 mmol) of diethyl amino diacetate, and 0.72 g (8.6 mmol) of NaHCO, in 30 mL of DMF was stirred at 100 °C for 6 hours. DMF was removed in vacuo and the residue was extracted with ether and washed with brine. The extract was dried over MgSO, and the concentrated residue was purified by column chromatography to give amino diester intermediate: ¹H NWR (CDCl₃) & 0.90 (q, 6H), 1.05-1.65 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55 (s, 4H), 3.95 (s, 2H), 4.1-4.2 (m, 5H), 5.05 (s, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (s, 6H), 7.8 (d, 1H).

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Step 3: Preparation of amino diacid

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0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.22 (t, 1H), 2.8 (8, ester (obtained from Step 2) and 0.232 g (5.52 mmol) 1H), 5.1 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 6H), 3.0 (t, 2H), 3.5 (s, 4H), 3.9 (s, 2H), 4.1 (d, title compound as a solid: mp 175 °C; 'H NMR (THF-d8) MgSO, and concentrated in vacuo to give the desired aqueous layer was extracted twice with ether, and the at 40 °C under N_2 for 4 hours. The reaction mixture Calc'd for C, H, N,O,S: C, 65.68; H, 7.25; N, 4.03; S, Calc'd for C, H, N, O, S: 695.3366. Found: 695.3359. Anal. 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS. combined extracts were washed with brine, dried over was diluted with ether and washed with 1% HCl. The of LiOH in 30 mL of THP and 30 mL of water was stirred 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62 A solution of 0.863 g (1.15 mmol) of dibenzyl

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Example 1428

(4R-cis) -4-[[4-[3,3-Dibutyl-7-(dimothylomino)-2,3,6,5-totrohydro-4-bydroxy-1,1-dioxido-1,1-dioxido-1.bonsothispin-5-yl]phonoxy]mothyl]-1-mothylpyridinium onlt with trifluoroscetic said (1,1)

Step 1: Preparation of picolyl intermediate

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idded. The reaction was stirred at ambient temperature rere washed with brine, dried over MgSO,, and filtered. for 17 hours. The reaction was quenched with 25 mL of 5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride picolinyl intermediate as a colorless solid: mp 95-98 To a stirred solution of 12.0 g (26.1 mmol) of 5hydrobenzothiepine-1,1-dioxide (obtained from Example reaction stirred at ambient temperature for one hour. silica gel chromatography (Waters-prep 500) using 60% 1402, Step 10) in 200 mL of DMF was added 1.4 g (60% filtered and concentrated in vacuo. Purification by extracted with diethyl ether. The ethereal extracts ethyl acetate/hexanes afforded 11.05 g (77%) of the solution of 4-picolyl chloride in diethyl ether was was treated with cold saturated NaHCO, solution and oil dispersion, 35 mmol) of sodium hydride and the washed with 4X250 mL water, brine, dried over MgSO. saturated NH,Cl, diluted with 600 mL ethyl acetate The reaction was cooled in an ice bath and the (4'-hydroxyphenyl)-7-(dimethylamino)tetra-

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°C; ¹H NWR (CDC1,) & 0.86-0.96 (m, 6H), 1.02-1.52 (m, 10H), 1.58-1.70 (m, 1H), 2.16-2.29 (m, 1H), 2.81 (g, 6H), 3.07 (ABq, J_M = 15.3, 49.6 Hz, 2H), 4.10 (d, J = 7.5 Hz, 1H), 5.15 (g, 2H), 5.50 (g, 1H), 5.94 (d, J = 2.7 Hz, 1H), 6.51 (dd, J = 2.4, 8.7 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 7.89 (d, G = 9.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 8.63 (dd, J = 1.6, d, G = 2.1), 7.14

Step 2: Preparation of quaternary salt

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reversed phase chromatography (Waters-Delta prep) using 60-55% water/acetonitrile afforded 0.304 g (60%) of the 2.4 Hz, 1H), 6.61 (dd, J = 2.5, 8.7 Hz, 1H), 7.02 (d, J 8.7 Hz, 1H), 8.14 (d, J = 6.3 Hz, 2H), 8.80 (d, J = 6.6 Hz, 2H). HRMS Calc'd for C,H4,N,O,S: 565.3100. Found: desired title compound as a colorless solid: mp 96-99 picolinyl intermediate (obtained from Step 1) in 10 mL 1.46 (8, 3H), 5.37 (8, 2H), 5.50 (8, 1H), 6.07 (d, Ja 5H), 3.09 (ABq, Ja = 15.0, 27.9 Hz, 2H), 4.11 (8, 1H), 8.7 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.90 (d, J = of acetonitrile and 3 mL of dichloromethane was added concentrated under a nitrogen stream. Purification by 137 mg (0.97 mmol) of iodomethans. The reaction was 10H), 1.57-1.70 (m, 1H), 2.12-2.27 (m, 1H), 2.84 (s, C; ¹H NMR (CDCl,) 8 0.85-0.95 (m, 6H), 1.03-1.52 (m, To a stirred solution of 0.41 g (0.74 mmol) of stirred at ambient temperature for 16 hours, then 565.3125.

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Example 1429

(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benxothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium, methanesulfonate (salt)

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9.02 (d, J. 6.6 Hz, 2H). HRMS Calc'd for C11H4N3O48: 0.66-0.76 (m, 6H), 0.85-0.95 (m, 1H), 0.95-1.35 (m, 5.78 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 2.5, 8.7 Hz, 24.0 Hz, 2H), 3.88 (B, 1H), 4.40 (B, 3H), 5.21 (B, 3H), off-white solid: mp 232-233.5 °C; 'H NMR (CDCl₁) & to give 6.14 g (79%). The filtrate was concentrated in 1.56 g (14.6 mmol) methanesulfonic acid methyl ester. picolyl intermediate (obtained from Example 1428, Step 565.3100. Found: 656.3087. Anal. Calc'd for 2H), 7.64 (d, J = 8.7 Hz, 1H), 8.0 (d, J = 6.6 Hz, 2H), 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.4 Hz, 1H), 2.56 (8, 3H), 2.63 (8, 6H), 2.91 (AB_q, J = 16.5, 9H), 1.42- 1.54 (m, 1H), 1.95-2.22 (m, 1H), 2.50 (s, (93%) of the desired title compound was obtained as an acetonitrile to give 1.09 g (14%). A total of 7.23 g vacuo and the residue crystallized from hot acetate. The solid was collected by vacuum filtration reaction was cooled and diluted with 50 mL of ethyl Heating was continued at 70 °C for 15 hours. The 1) in 140 mL of acetonitrile heated at 70 °C was added To a stirred solution of 6.5 g (11.8 mmol) of

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C₁:H₄:N₂O₂S₂: C, 61.79; H, 7.32; N, 4.24; S, 9.70 Found: C, 61.38, H, 7.47; N, 4.22; S, 9.95.

Example 1430

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(4R-cis)-6-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-bensothiepin-5-yl]phenoxy]methyl]-2-pyridinepropanoic acid

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30 25 20 15 4.10 (d, 2H), 4.65 (s, 2H), 5.20 (s, 2H), 5.45 (s, 1H), 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, intermediate as an oil (0.70g, 55%): 1H NMR (CDCl₃) & EtOAc/Hexane gave 0.75 g (55%) of the picolyl chloride purification through silica gel, eluting with 25% filtered and concentrated in vacuo. Chromatographic mL). The organic layers were dried over MgSO₄, diluted with ether and washed with water and brine (30 magnetic stirrer. The reaction was heated to reflux 2,6-bischloromethylpyridine (1.29, 10.8 mmol). The mmol), tetrabutylammonium iodide (0.1g, 0.2 mmol) and acetone (50 mL) was added anhydrous K₂CO, (0.45g, 3.2 2.1 mmol, obtained from Example 1402, Step 10) in Step 1: Preparation of picolinyl chloride intermediate flask was equipped with nitrogen gas adapter and for overnight. After 18 hours, the reaction was (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1g, To a solution of 5-(4'-hydroxyphenyl)-7-

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5.95 (8, 1H), 6.50 (d, 1H), 7.0 (d, 2H),7.35-7.50 (m, 4H), 7.70-7.85 (m, 2H).

Step 2: Preparation of pyridinyl malonate intermediate

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mL) and sodium hydride (0.13g, 3.3 mmol) were placed in concentrated. The residue was purified by C-18 reversed (8, 1H), 5.97 (8, 1H), 6.96-7.10 (m, 3H), 7.20-7.32 (m, Dibenzyl malonate (1.42g, 5.01 mmol) in DMF (20.0 (d, 1H), 4.16 (t, 1H), 5.02(8, 2H), 5.08 (8, 4H), 5.44 nitrogen gas adapter and magnetic stirrer. The picolyl heated at 90°C for overnight. The reaction was cooled ind extracted with 5% HCl with methylene chloride and gave pyridinyl malonate intermediate as a white foamy phase column eluting with 50% acetonitrile/water and 1H), 2.80 (8, 6H) 3.05 (ABq, 2H), 3.22 (d, 2H), 4.05 a dry three-neck flask. The flask was equipped with solid (1g, 71%): 1H NMR (CDC1,) 8 0.84-0.95 (m, 6H), chloride intermediate (1g, 1.67 mmol) was added and 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, organic layers were dried over MgSO,, filtered and washed with water (25 mL), and brine (50 mL). The (2H), 7.5 (t, 1H), 7.9 (d, 1H).

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Step 3: Preparation of pyridinyl acid

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The pyridinyl malonate intermediate (0.6g, 0.7 mmol, obtained from Step 2), THF/water (25.0 mL, 1:1) and lithium hydroxide monohydrate (0.14 g, 3.4 mmol) were placed in a 100 mL round-bottom flack. The reaction was stirred at ambient temperature overnight. After 18 hours, the reaction was extracted with 1% HCl and ether and then washed with water (20 mL) and brine (30 mL). The organic layers were dried over MgSo,, filtered and concentrated in vacuo gave the desired title compound as a white solid (0.44g, 90%): mp 105-107 °C; ¹H NMR (CDCl.) & 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s,

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6H),3.05 (m, 2H), 3.10 (ABq, 2H), 3.22 (m, 2H), 4.05 (8, 1H), 5.30 (8, 2H), 5.50 (8, 1H), 5.97 (8, 1H), 6.50 (4, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for C₁H₄N₃O₄S: 623.3155. Found: 623.3188.

cample 1431

(4R-cis)-N-(Carboxymothyl)-N-[[6-[13,3-dibutyl-7-(dimethylamino)-2,3,4,5-totrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phonoxy]mothyl]-2-pyridinyl]methyl]glycino

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Step 1: Preparation of pyridinyl diester intermediate

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A mixture of diethyl aminodiacetate (8g, 68 mmol) and sodium carbonate (0.63g, 5.9 mmol) was treated with picolyl chloride intermediate (0.72g, 1.2 mmol, obtained from Example 1430, Step 1), and stirred at 160 °C for three hours. The reaction was cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts were dried over MgSO, filtered and concentrated in vacuo. The residue was purified by distillation in the Kugelrohr to give pyridinyl diester intermediate as a yellowish foamy solid (0.72g, 80%): ¹H NMR (CDCl,) & 0.84-0.95 (m, 6H), 1.02-1.5 (m, 16H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (Abg, 2H), 3.70 (s, 4H), 4.2-4.4 (m, 6H), 5.30 (s, 2H), 5.56 (s, 1H), 6.60

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(t, 1H), 7.95 (d, 1H). HRMS. Calc'd for C41H,N3O,S: (d, 1H), 7.10 (d, 2H), 7.50 (m, 3H), 7.61 (d, 1H), 7.80 752.3945. Found: 752.3948.

Step 2: Preparation of pyridinyl diacid

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6H), 3.10 (ABQ, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 155 °C; ¹H NMR (CDCl₃) & 0.84-0.95 (m, 6H), 1.02-1.5 (m, title compound as a white solid (0.44g, 90%): mp 153and washed with 1% HCl, water (20 mL), and brine (30 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 filtered and concentrated in vacuo to give the desired mL). The organic layers were dried over MgSO, (d, 1H), 7.8-7.9 (m, 2H). (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 hours). The reaction mixture was diluted with ether (25.0 mL, 1:1) was stirred at 40 °C overnight (18 hydroxide monohydrate (0.18 g, 4.5 mmol) in THF/ water (0.7g, 0.93 mmol, obtained from Step 1), and lithium A mixture of pyridine-aminodiacetate intermediate

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HRMS. Calc'd for C,,H,,N,O,S: 696.3319. Found:696.3331

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bensothiepin-5-yl]phenoxy]ethoxy]athyl]propanedioic 2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-(48-cis) - [2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-

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Step 1: Preparation of bromoethyl ether intermediate

7.4 (d, 2H), 7.9 (d, 1H). 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.95 (d, 2H), 3.5 (t, 2H), 3.9 (m, 4H), 4.1 (d, 1H), 4.2 (d, 2H), 1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), ether intermediate: 'H NMR (CDCl₃) & 0.90 (q, 6h), 1.05purified by column chromatography to give bromoethyl was dried over MgSO, and the concentrated residue was DMF was removed in vacuo and the residue was extracted continued at ambient temperature under N2 overnight. mmol) of bis(2-bromoethyl)ether, and stirring was for 30 min. To the solution was added 13.2 g (54.38 resulting solution was stirred at ambient temperature mmol) of 5-(4'-hydroxyphenyl)-7disp) of NaH in 28 mL of DMF was added 2.0 g (4.35 with ethyl acetate and washed with brine. The extract (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the To a stirred solution of 0.192 g (4.785 mmol, 60%

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Step 2: Preparation of diester intermediate

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g (4.68 mmol) of dibenzyl malonate (Aldrich), and the chromatography to give the diester intermediate: 'H NMR brine. The extract was dried over MgSO,, and the overnight. Solvent was removed in vacuo and the residue for 15 min, followed by the addition of 0.95 g (1.56 in 45 mL of THF and 15 mL of DMF at 0 °C was added 1.33 was extracted with methylene chloride and washed with Step 1). The mixture was stirred under N, at 80 °C mmol) of bromoethyl ether intermediate (obtained from resulting solution was stirred at ambient temperature 3H), 2.8 (s, 6H), 3.0 (q, 2H), 3.6 (t, 2H), 3.7 (m, (CDCl₃) 8 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2-2.3 (m, concentrated residue was purified by column To a mixture of 94 mg (2.34 mmol, 60% disp) of NaH

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3H), 4.1 (m, 3H), 5.1 (s, 4H), 5.42 (s, 1H), 5.9 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3 (m, 10H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 3: Preparation of diacid

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A suspension of 0.761 g (0.935 mmol) of the diester intermediate (obtained from Step 2) and 35 mg of 104 Pd/C in 25 mL of ethanol and 5 mL of THF was aditated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 119.5 °C; ¹H NNR (THF-d8) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.1 (q, 2H), 2.25 (t, 1H), 2.8 (s, 6H), 1.05-1.65 (m, 11H), 4.15 (t, 2H), 3.58 (s, 1H), 6.05 (s, 1H), 6.55 (d, 1H), 6.98 (d, 2H), 7.42 (d, 2H), 7.8 (d, 1H). HWMS. Calc'd for C,H,NO,S; 632.2893. Found: 632.2892. Anal. Calc'd for C,H,NO,S; C, 62.54; H, 7.47; N, 2.21; S, 5.06. Found: C, 61.75; H, 7.56; N, 2.13; S, 4.92.

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Example 1433

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(4R-cio)-c.[[4-[3,3-Dibutyl-7-(dimethylomino)-2,3,4,5-tetruhydro-4-hydroxy-1,1-dioxido-1-benzethiepin-5-yl]phonoxy]methyl]-w-methoxypoly(oxy-1,2-ethonodiyl)

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Step 1: Preparation of monomethyl PEG mesylate intermediate

To a solution of 20 g of monomethyl ether PBG in 100 mL of methylene chloride was added 2.2 g (22 mmol) of triethyl amine, and to the resulting solution at 0°C was added dropwise 2.5 g (22 mmol) of methanesulfonyl chloride. The resulting solution was stirred overnight at ambient temperature, and the triethyl amine hydrochloride was filtered off to give the monomethyl PBG mesylate intermediate which was used in the next Step without further purification and characterization.

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Step 2: Preparation of polyethylene-linked

benzoth1epene

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mesylate PEG intermediate (obtained from Step 1) in 5.5 A mixture of 38 mg (1.52 mmol 95%) of NaH and 0.7 (obtained from Example 1402, Step 10) in 5.5 mL of DMP «as stirred at ambient temperature under N, for 30 min. compound as an oil: ¹H NMR (CDCl₃) & 0.9 (q, 6h), 1.05and the residue was extracted with methylene chloride 1.65 (m, 11H), 2.2 (t, 1H), 2.8 (8, 6H), 3.0 (q, 2H), 3.4 (8, 4H), 3.5-3.85 (m, 95H), 4.1 (8, 1H), 4.15 (t, overnight under N, at 50 °C. DMF was removed in vacuo To the solution was added 0.55 g (0.51 mmol) of the 2H), 5.5 (B, 1H), 6.05 (B, 1H), 6.6 (d, 1H), 6.9 (d, (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide MgSO,, and the concentrated residue was purified by and washed with brine. The extract was dried over mL of DMF, and the resulting solution was stirred column chromatography to give the desired title g (1.52 mmol) of 5-(4'-hydroxyphenyl)-7-IH), 7.4 (d, 2H), 7.9 (d, 1H).

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Preparation of

gave a white solid (0.269g, 56%). 1H NWR (CDCl3) & mL) was added, and the mixture was washed with H₂O (2x4 magnetic stirrer, and cooled to 0 °C. A solution of 3-1H), 7.23 (d, J = 7.8 Hz, 1H), 7.34-7.39 (m, 2H), 7.54 = 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.7 Hz, 1H), 6.65 (s, 1H), 4.33 (t, J = 6.0 Hz, 2H), 5.50 (8, 1H), 5.99 (d, J 0.87-0.93 (m, 6H), 1.05-1.70 (m, 11H), 2.14 (t, J=6.3eluting with 20% EtOAc/hexane and concentrated in vacuo mL), dried (MgSO₄), filtered and concentrated in vacuo. CH₂Cl₂/ THF) was added. After 3.5 hrs, toluene (3.0 chloropropyl chloroformate (1.440g, 1.10 mmol, 12% in reaction flask was purged with N, equipped with were combined in a 10 mL round-bottom flask. The Example 1398 (0.380g, 0.828 mmol), sodium hydroxide H). Calc'd for C30H44N2O5SCl: 579.2659. Found: (d, J = 7.2 Hz, 1H), 7.89 (d, 8.7 Hz, 1H). HRMS (M +2H), 3.64 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 7.5 Hz, Hz, 2H), 2.15-2.25 (m, 1H), 2.81 (s, 6H), 3.07 (ABq, Purification by flash chromatography on silica gel (0.35 mL; 0.875 mmol, 10% in H₂O) and toluene (0.50 mL) The 3-aminobenzothiepene prepared in Step 5 of

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Example 1435

Preparation of:

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15 10 25 20 mmol) and acetonitrile (1.0 mL) were combined in a 10 with ethyl ether (10.0 mL). The precipitate was diazabicyclo(2.2.2)octane (0.0490g, 0.437 mmol) was 37 °C. A solution of the product of Example 1434 with N_2 , equipped with magnetic stirrer, and heated to mL round-bottom flask. The reaction flask was purged was dissolved in acetonitrile (2.0 mL) and precipitated 3.30-3.50 (m, 8H), 4.10 (s, 1H), 4.21 (t, J = 5.4 Hz, 2.76 (8, 6H), 3.10 (m, 2H), 3.17 (t, J = 7.2 Hz, 6H), 1.16 (t, J = 6.6 Hz, 2H), 1.78 (m, 1H), 2.12 (m, 3H), to give a white solid (0.185g, 62%). mp 218.0-225.0 °C; method was repeated, followed by concentrated in vacuo filtered to yield a white solid. This trituration to R.T. and concentrated in vacuo. The crude product added. After 24 hrs, the reaction mixture was cooled (0.0200g, 0.178 mmol) was added. After 64 hrs, 1,4-2H), 5.31 (8, 1H), 6.10 (8, 1H), 6.55 (d, J = 7.2 Hz, 1H NMR (CD3OD) 8 0.90 (m, 6H), 1.05-1.55 (m, 10H), added. After 2.5 hrs, 1,4-diazabicyclo(2.2.2)octane (0.250g, 0.432 mmol) in acetonitrile (2.50 mL) was 1,4-Diazabicyclo(2.2.2)octane (0.0785g, 0.700

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1H), 7.25 (d, J = 6.9 Hz, 1H), 7.33-7.42 (m, 2H), 7.56
(e, 1H), 7.76 (d, J = 9.0 Hz, 1H). HRMS. Calc'd for C36H5SN4058Cl: 655.3893. Found: 655.3880.

Example 1436

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Preparation of:

Step 1. Preparation of:

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3-Chloromethylbenzoyl chloride (2.25 mL/15.8 mmol) and acetone (8.0 mL) were combined in a 25 mL roundbottom flask. The reaction flask was cooled to 0°C, and an aqueous solution of sodium azide (1.56g in 5.50 mL/24.0 mmol) was added. After 1.5 hrs, the reaction mixture was poured into ice water (80.0 mL), extracted with ethyl ether (2x25 mL), dried (MgSO₄), and concentrated in vacuo to give a coloriess oil (2.660g, 86\$). Then NRR (CDC13) & 4.62 (8, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.65 (g, 1H).

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632.2901. Found: 632.2889.

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Step 2.

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reflux. After 0.5 hrs, the reaction mixture was cooled 2.25 hrs, the mixture was heated to 50 °C. After 0.75 [lash chromatography on silica gel eluting with 20-30% (m, 11H), 1.85 (d, 6.3 Hz, 1H), 2.27 (m, 1H), 2.76 (s, 2H), 5.42 (8, 1H), 6.07 (8, 1H), 6.99 (d, J = 7.5 Hz), foamy solid (0.309g, 62%). 1H NMR (CDC13) 8 0.71 (t, 6H), 3.15 (t, 2H), 4.17 (d, J = 6.6 Hz, 1H), 4.48 (s, 3-Chloromethylbenzoyl azide (0.142g, 0.726 mmol) bottom flask. The reaction flask was purged with N, equipped with magnetic stirrer, and heated to 110 °C. hrs, 3-chloromethylbenzoyl azide (0.025g, 0.128 mmol) J = 5.4 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H), 1.03-1.60 7.86 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 8.17 (s, 1H). After 2 hrs, the reaction mixture was cooled to R.T, and toluene (2.0 mL) were combined in a 10 mL round-7.18-7;26 (m, 2H), 7.30-7.41 (m, 3H), 7.63 (s, 1H), Example 1398 (0.365g, 0.796 mmol) was added. After EtOAc/hexane and concentrated in vacuo gave a white and the 3-aminobenzothiepene prepared in Step 5 of to R.T. and concentrated in vacuo. Purification by was added, and the reaction mixture was heated to HRMS (M + Li). Calculated for Cj4H44N3O4SClLi;

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Example 1437

Preparation of:

65.06; H, 7.64; N, 9.48; S, 4.34; Cl, 4.80. Found: C, 702.4064. Anal. Calculated for C40H56N5O4SCl: C, Calculated for C40H56N5O4SCl: 702.4053. Found: 2H), 7.58 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H). HRMS. 7.23 (d, J = 6.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.47 (m, 8 0.88 (m, 6H), 1.03-1.55 (m, 10H), 1.76 (m, 1H), 2.11 with ethyl ether, and dried in vacuo to yield a white solid (0.250g, 80%). . mp 246.0-248.0 OC; 1H NMR (CD3OD) was added, and the precipitate was filtered, washed white precipitate had had formed. Ethyl ether (6.0 mL) acetonitrile (2.70 mL) was added. After 2.5 hrs, a the product of Example 1436 (0.262g, 0.418 mmol) in N, and equipped with magnetic stirrer. A solution of round-bottom flask. The reaction flask was purged with and acetonitrile (1.00 mL) were combined in a 10 mL 64.90; H, 7.77; N, 9.42; S, 4.16; Cl, 4.89. (dd, J = 8.7, 1.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), (8, 1H), 4.39 (8, 2H), 5.31 (8, 1H), 6.11 (8, 1H), 6.52 (m, 1H), 2.74 (e, 6H), 3.11 (m, 8H), 3.37 (m, 6H), 4.12 1,4-Diazabicyclo(2.2.2)octane (0.157g, 1.40 mmol)

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Examples 1438 - 1454

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The compounds of Examples 1438 through 1454 can be prepared in accordance with one or more of the synthetic schemes previously disclosed in this application or using methods known to those skilled in the art.

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Example 1455

Preparation of:

1H), 2.18 (bt, 1H), 2.34 (a, 2H), 2.78 (a, 6H), 3.04 1.05-1.49 (m, 14H), 1.18 (t, J = 6.8 Hz, 2H), 1.59 (bt, Concentrated in vacuo to give a white solid the precipitate (TLC: S10,/80% EtOAc/hexanes). precipitate and filtered. This precipitation procedure and ethyl acetate (0.057 mL/4 drops), cooled to white solid was dissolved in hot ethyl ether (2.0 mL) evaporated to dryness with a N, purge. The resulting (ABq, 2H), 3.35-3.80 (m, 625H), 4.09 (d, J = 7.2 Hz, (0.0838g/51%). 1H NWR (CDCl3) d 0.82-0.90 (m, 6H), was repeated until no starting material was detected in reaction mixture was transferred to a 2 mL vial and aminobenzothiepine of step 5 of Example 1398 8 mm NMR tube. The tube was purged with N2. After 72 (0.0077g/0.017 mmol) was added. After 24 hrs, the 24 hrs, an additional aliquot of the 3hrs, the reaction mixture was heated to 50 °C. After Alabama 35801), and CDCl, (0.7 mL) were combined in an Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, (Methoxy-PEG-NCO, MW 5000, purchased from Shearwater (0.0165g/0.0360 mmol), M-NCO-5000 (0.150g/0.30 mmol) The 3-aminobenzothiepine of step 5 of Example 1398

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data also verified desired product. Hz, 1H), 7.31 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H). Mass spectroscopy 1H), 6.47 (dd, J = 6.4, 3.2 Hz, 1H), 7.07 (d, J = 7.62H), 5.42 (s, 1H), 5.78 (s, 1H), 6.04 (d, J = 1.6 Hz,

Example 1456

Preparation of

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remove tetrahydrofuran. The residual aqueous solution at 45 °C for 3 days and concentrated in vacuum to 25 ml of tetrahydrofuran, and 25 ml of water was held mixture of this residue, 0.8 g of lithium hydroxide, distilled at 0.5 torr at 120 °C to remove excess 1), 11.45 g of diethyl iminodiacetate, and 1.14 g of was dried (MgSO,) and concentrated in vacuum. The and extracted with CH₂Cl₂ (2x50 ml). The CH₂Cl₂ layer was diluted with 25 ml of water and acidified to pH 2 diethyl iminodiacetate to give 1.0 g of a residue. A concentrated in vacuum. The residue was kugelrohr diluted with brine and extracted with CH2Cl2. The CH2Cl2 sodium carbonate was held at 160 °C for 3.5 hours, 4-R-hydroxybenzothiepine-1,1-dioxide (Example 32, Step bromoethoxyethoxy)phenyl-3,3-dibutyl-7-dimethylaminolayer was washed with brine, dried (MgSO,) and A mixture of 0.845 g (10.7 mmol) of 5-R-[4-(2-

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to give 0.86 g of solid, MS (negative FAB), m/e 685 (M* triturated with ether. The precipitate was collected residual solid was dissolved in hot CH,Cl, and + Na).

Example 1457

Preparation of:

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of desired 5-(4'-. 005 ğ A solution hydroxyphenyl) - 7-

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(Example 1402, Step 10) (1.09 mmol)in 5 ml of dimethylformamide was added via a syringe to a stirred solution of 36 mg of 95% NaH (1.41 mmol) in 5 mL of The resulting solution was stirred at -10 °C for 30 minutes. A solution of 1,25 g of 1,5-dibromopentane (5.45 mmol) in 5 mL of dimethylformamide was then added. The mixture was stirred at -10 °C for another 30 The reaction mixture was quenched The ethyl acetate layer. was dried over MgSO, and minutes and allowed to warm up to room temperature and with water at 0 °C and extracted with ethyl acetate. dimethylformamide at -- 10 °C in an acetone-dry ice bath. The crude product (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide concentrated in vacuo. stirred for 1 hour.

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2.22 (m, 1H), 2.82 (s, 6H), 3.08 (Abq, 2H), 3.46 (t, J 5.49 (8, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = of the bromide =6.9 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 4.1 (s, 1H), chromatographed on Bilica gel column with 15% ethyl intermediate (71%) as a white solid: 1H NMR (CDC13) 80.91 (m, 6H), 1.20-1.67 (m, 13H), 1.80 -2.00 (m, 4H), 9.0 Hz, 2.7 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). Ē to give 470 acetate/hexane

tris(trimethylsilyl) phosphite was refluxed at 100 °C overnight. The reaction mixture was cooled to room temperature and 30 mL of 50% methanol/water solution (8, 1H), 5.48 (8, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.53 A stirred solution of 400 mg of the browide was added. The mixture was stirred at room temperature for 5 hours. The mixture was concentrated in vacuo and the resulting aqueous solution was extracted with CH,Cl,. The CH,Cl, solution was dried over MgSO, and concentrated in vacuo to yield a yellowish oil. The oil was dissolved in CH,Cl, and triturated with ethyl acetate to give 202 mg of the desired product (50%) as a white solid. 1H NMR (CDCl3) & 0.90 (m, 6H), 1.14-2.10 (m, 21H), 2.81 (s, 6H), 3.07 (ABq, 3.98 (m, 3H), 4.11 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), mmo] 99.0) intermediate

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7.40 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H).

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Example 1458

Preparation of:

A mixture of 0.325 g (1.78 mmol) of 5mercaptotetrazoleacetic acid sodium salt, 1.0 g of
potassium carbonate, and 30 ml of dimethylformamide
was stirred for 2 hours then was charged with 1.06 g
(1.74 mmol) of 5-R-[4-(5-bromopentoxy)phenyl-3,3dibutyl-7-dimethylamino-4-R-hydoxybenzothiepine-1,1dioxide (Example 1413, Step 1). The reaction mixture
was stirred for 20 hours at room temperature and

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concentrated in vacuum. The residue was stirred in ether and water (100 ml each). A waxy material resulted that was insoluble to both the ether and aqueous layers. The waxy material was combined with the aqueous layer and was acidified with concentrated HCl and extracted with CH₂Cl₂. The CH₂Cl₃ layer was dried (MgSO₄) and concentrated in vacuum to yield 1.35 g of a syrup, MS (negative FAB), m/e 686 (M'-1); NMR (CDCl₃), 8.0 (d, 1H, 7 Hz), 7.50 (d, 2H, 7 Hz), 7.00 (d, 2H, 7 Hz), 6.7 (d, 1H, 7 Hz), 6.2 (s, 1H), 5.6 (s, 1H), 5.15 (s, 2H), 4.2 (s, 1H), 4.1 (s, 2H), 3.7(s, 2H), 3.1-3.2 (ABq, 2H), 2.9 (s, 6H), 2.3 (t, 2H, 8 Hz), 0.9-2.0 (m, 24H).

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Example 1459

Preparation of:

(4R-cis)-1-[N-[3-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothlepin-5-yl]]phenylacetamido]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

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A solution of the aniline derivative prepared in Example 1398, Step 5 (1.0 g, 2.2 mmol) in dichloromethane (10 mL) at 0 °C under N, was treated with N,N-di-isopropyl-ethylamine (0.53 mL, 3.1 mmol,

The white crystals were collected and washed with hexane (50 mL) to give a chloroacetyl intermediate (0.74 g, 63%) as a pale 1.4 eq.), followed by the dropwise addition of a 10 minute period. The reaction mixture was stirred and the aqueous layer was extracted with ethyl acetate $(2 \times 25 \text{ mL})$. The combined organic extracts were washed oil which yellow solid: ¹H NMR (CDCl,) & 0.95 (m, 6H), 1.15-1.71 (br m, 11H), 2.24 (m, 1H), 2.85 (8, 6H), 3.12 (ABq, J chloroacetyl chloride (0.21 mL, 2.6 mmol, 1.2 eq.) over and allowed to warm to 25 °C over a 2 hour period. The mixture was quenched by the addition of 1N HCl (25 mL) with saturated aqueous sodium bicarbonate (2 x 25 mL) 4.23 (s, 2H), 5.57 (s, 1H), 6.05 (m, 1H), 6.58 (dd, J = 8.9, 2.4 Hz, 1H), 7.37-7.49 (m, 2H), 7.79 (d, J = 8.5 (5.0 Hz, J = 48.8 Hz, 2H), 4.15 (d, J = 6.2 Hz, 1H), and brine (30 mL), and were dried (MgSO,) Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H), 8.30 (s, 1H) a pale yellow erystallized upon standing. concentrated to give

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*AB treated with diazabicyclo[2.2.2]octane (DABCO, 10 The mixture was allowed to resulting white solid was collected and washed with A solution of the chloroacetyl intermediate (26 mg, 0.05 mmol) in acetonitrile (1 mL) at 50 °C under N_3 hours. The reaction mixture was allowed to cool to 25 was dissolved in warm acetonitrile and tert-butyl stand overnight during which time crystals formed. The tert-butyl methyl ether (25 mL) to give the title compound (17 mg, 55%) as a white crystalline solid: 4 ng, 0.09 mmol, 1.8 eq.) and atirred at 50 °C for 2 of and was concentrated to form a residue. The residue NAGR (CDCl,) 8 0.88 (m, 6H), 1.08-1.42 (br m, 8H), 1.45-1.80 (br m, 4H), 2.14 (m, 1H), 2.75 (s, 6H), 3.08 (ABg, J = 15.1 Hz, J = 34.3 Hz, 2H), 3.21 (m, 6H), 3.79 (m, 5H), 4.12 (8, 1H), 4.62 (8, 2H), 5.41 (8, 1H), 5.99 (m, methyl ether was added.

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1H), 6.48 (d, J = 8.9 Hz, 1H), 7.33 (m, 1H), 7.70 (br s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 11.3 (s, 1H); HRMS. Calc'd for C₁₄H_{B1}N₄O₄S: 611.3631. Pound: 611.3638.

Example 1460

Preparation of:

Step 1: Preparation of diethyl iminodiacetatosulfonamoyl chloride

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Sulfuryl chloride (27.552g/204.1 mmol) and chloroform (50.0 mL) were combined in a 250 mL round-bottom flask. The reaction flask was purged with N₃,

organic layer was separated, washed with 10% ag. HCl solution below 20 °C. After the addition was 4.23 (q, 4H), 4.38 (s, 4H). HRMS (EI/M + H). Calc'd liquid (5.706g/20%). 1H NMR (CDCl3) & 1.30 (t, 6H), filtered and concentrated in vacuo to give an amber (50 mL) and chilled water (2 x 50 mL), dried (CaCl₃), was poured into ice water (100 mL) and mixed well. The room temperature. After 2 hours, the reaction mixture completed, the reaction mixture was allowed to warm to dropwise while maintaining the temperature of the and triethylamine (10.112g/99.9 mmol) was added solution of diethyl iminodiacetate (18.902g/99.9 mmol) equipped with magnetic stirrer, and cooled to 0 °C. for C8H15NO6SCl: 288.0309. Found: 288.0300.

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Step 2: Preparation of:

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diethyl iminodiacetato-sulfonamoyl chloride prepared in After 18 hours, additional diisopropylethylamine purged with N, and equipped with magnetic stirrer. in a 25 mL round-bottom flask. The reaction flask was step 1 of this Example (0.650g/2.260 mmol) were combined diisopropylethylamine (0.148g/1.148 mmol), and the (0.074g/0.574 mmol) and diethyl iminodiacetato-(0.503g/1.097 mmol), toluene (5.00 mL), The 3-aminobenzothiepine of step 5 of Example 1398

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concentrated in vacuo gave a white solid (0.349g/45%) silica gel eluting with 30% ethyl acetate/hexane and in vacuo. Purification by flash chromatography on aqueous NaCl (25.0 mL), dried (MgSO,), and concentrated After 24 hours, dichloromethane (75.0 mL) was added. sulfonamoyl chloride (0.181g/0.628 mmol) were added The mixture was washed with aqueous NaHCO, (25.0 mL), 1H NMR (CDC13) 8 0.91 (m, 6H), 1.10-1.70 (m, 10H),

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2.81 (s, 6H), 3.09 (dd, J = 36.6, 15.3 Hz, 2H), 4.11-Calc'd for C34H52N3O982: 710.3145. Found: 710.3158. 6.51 (dd, J = 8.7, 2.4 Hz, 1H), 7.24-7.38 (m, 5H), 7.44 4.24 (m, 9H), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 1.27 (t, J = 7.2 Hz, 6H), 1.90 (m, 1H), 2.21 (m, 1H), (bs, 1H), 7.90 (d, J = 9.0 Hz, 1H). HRMS (BSI/M + H).

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Step 3: Preparation of Title Compound:

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35 ä 25 20 NMR (CD3OD) & 0.89 (m, 6H), 1.05-1.50 (m, 10H), 1.68 ether gave a white crystalline solid (0.109g/53%). 1H concentrated in vacuo. Precipitation from After 18 hours, a white precipitate had formed, which mL), and acidified with aqueous 3.0 N HCl (0.40 mL). magnetic stirrer. A solution of LiOH.H₂O (0.030g/0.715 reaction flask was purged with N_2 and equipped with mL) were combined in a 10 mL round-bottom flask. The Example (0.224g/0.316 mmol) and tetrahydrofuran (1.00 (m, 1H), 2.16 (m, 1H), 2.89 (8, 6H), 3.13 (m, 2H), 4.07 recrystallization from t-butyl methyl ether/diethyl acetonitrile/diethyl ether/hexanes and was filtered, washed with water (2.0 mL) and aqueous mixture was washed with diethyl ether (4 \times 4.0 After 30 minutes, water (6.0 mL) was added. The mmol) in water (0.50 mL) was added. After 4 hours, (s, 4H), 4.18 (s, 1H), 5.45 (s, 1H), 6.52 (s, 1H), 6.93 additional LiOH.H,O (0.015g/0.357 mmol) was added. The benzothiepine prepared in step 2 of this

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(d, J = 8.7 Hz, 1H), 7.19 (d, J = 6.6 Hz, 1H), 7.35 (m, 3H), 7.70 (bs, 1H), 7.99(d, J = 8.7 Hz, 1H) HRMS (ESI/M + H). Calc'd for C30H44N3O9S2: 654.2519. Found: 654.2512.

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As one skilled in the art will appreciate, where a non-enantioselective synthesis is employed in any of the above examples and an enantiomeric-enriched final product is desired, the enantiomeric-enriched final product can be obtained by use of chiral chromatographic purification at an appropriate stage of the synthesis. For example, where the synthesis proceeds through the intermediate 5-(4'-methoxyphenyl)-7-(dimethylamino) terrahydrobenzothiepine-1,1-dioxide which is then demethylated to form the intermediate 5-(4'-hydroxyphenyl)-7-(dimethylamino)-

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'''y ''nyucxypueny1)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the 5-(4'methoxypheny1)-7-

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(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide preferably is subjected to a chiral chromatagraphic purification step prior to demethylation. The separated enantiomer is then demethylated to yield the enantiomeric-enriched intermediate 5-(4'-hydroxyphenyl)-7-

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(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide for use in the next step of the synthesis. By way of further illustration, chiral chromatographic purification could be performed immediately prior to Step 7 of Example 1398a using a column such as a Chiralpak AD column with an ethanol/heptane mobile phase (5%-10% ethanol v/v) at a wavelength of 220 nm. The separated enantiomer is then used as an intermediate in Step 7 of the synthesis thereby resulting in an enantiomeric-enriched final product.

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Similarly, where the synthesis proceeds through the intermediate 5-(3'-methoxyphenyl)-7-

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(dimethylamino) - tetrahydrobenzothiepine-1,1-dioxide which is then demethylated to form the intermediate 5-(3'-hydroxyphenyl)-7-

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(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the 5-(3'-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide preferably is subjected to a chiral chrowategraphic purification step prior to demethylation. The separated enantiomer is then demethylated to yield the enantiomeric-enriched intermediate 5-(3'-hydroxyphenyl)-7-(dimethylamino)-tetrahydrobenzothiepine-1,1-dioxide for use in the next step of the synthesis. By way of further illustration, chiral chromatographic purification could be performed immediately prior to Step 9 of Example 1400 with the separated enantiomer then used as the intermediate in Step 9 of the synthesis thereby resulting in an enantiomeric-enriched final product.

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Further, chiral chromatographic purification can be used where the synthesis proceeds through the intermediate 5-(3' or 4'-aminophenyl)-7-(dimethylamino)tetrahydro-benzothiepine-1,1-dioxide, such as in the Example Corresponding To Scheme XII. Por example, chiral chromatographic purification could be performed immediately following Step 5 of the Example Corresponding To Scheme XII to yield the enantiomericentiched intermediate 5-(3' or 4-aminophenyl)-7-(dimethylamino)tetrahydroherzothiamino)

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enriched intermediate 5-(3' or 4-aminophenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide for use in the next step of the synthesis.
Alternatively, an enantioselective synthesis, such

as the one described in Example 1461 below, could be used to provide the desired enantiomeric-enriched 5-(3'or 4'-aminophenyl)-7-

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(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide intermediate.

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Example 1461

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Preparation of:

Step 1: Preparation of triflic intermediate

A solution of 10.17 g (22.13 mmol) of 5-(4'-hydroxyphenyl)-7-

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5.42 (8, 1H), 5.88 (d, J = 2.1 Hz, 1H), 6.59 (dd, J =9, 87.2%); ¹H NMR (CD₃OD) & 0.85-1.0 (m, 6H), 1.0-1.15 Hz, 1H), 2.79 (8, 6H), 3.1-3.2 (que, 2H), 4.05 (8, 1H), the desired title compound as a pale yellow foam (11.42 on silica gel (25% ethyl acetate in hexane) to afford evaporated. The residue was purified by chromatography each). The combined organics were washed with 2N HCl mL) at 0° C under nitrogen gas was treated with triflic (m, 10H), 1.76 (t, J = 12.6 Hz, 1 H), 2.12 (t, J = 13 then dried over MgSO, filtered and the solvent and extracted three times with ethyl acetate (45 mL temperature for 21 hours. The pyridine was removed in dropwise. Upon completion of the addition, the bath (100 mL), 10% CuSO, (100 mL) and brine (100 mL), and vacuo, the resulting oil was taken up in water (100 mL) was removed and the reaction stirred at room anhydride (4.1 mL, 24.4 mmol, 1.1 equivalents) (prepared in Step 7 of Example 1398a) in pyridine (42 (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide

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8.9, 2.1 Hz; 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (d, J

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= 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.66 (e, 1H), 7.77 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of Imine

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H). 7.52 (m, 7H), 7.52-7.68 (m, 2H), 7.71 (d, J = 7.9 Hz, J = 9:1, 2.7 Hz, 1H), 6.74 (d, <math>J = 8.1 Hz, 1H), 6.801H), 5.17 (8, 1H), 5.92 (d, J = 2.2 Hz, 1H), 6.54 (dd 6.6 mL (39.4 mmol, 2.0 equivalents) of benzophenone 2.0 equivalents) in 114 mL of tetrahydrofuran was added mmol, 12 mol%) and cesium carbonate (8.86 g, 27.2 mmol, acetate (433 mg, 1.93 mmol, 10 mol*), racemic 2,2'-bistriflate (prepared in Step 1 above), palladium (II) (br s, 1H), 7.0-7.12 (m, 2H), 7.15-7.25 (m, 3H), 7.35-(m, 1 H), 2.78 (B, 6H), 2.98-3.15 (Q_{AB}, 2H), 3.88 (B, (CDOD₃) 8 0.8-1.45 (m, 16H), 1.6-1.75 (m, 1H), 1.9-2.05 in vacuo providing 19.11 g of a deep red foam: 'H NMR hours, filtered through celite and the solvent removed imine. (biphenylphosphenyl)-1,1'-binaphthyl (1.41 g, 2.26 To a solution of 11.41 g (19.28 mmol) of the The mixture was stirred at reflux for four

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Step 3: Preparation of Aniline

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To a solution of 19.1 g (theoretically 19.3 mmol) of the crude imine (prepared in Step 2 above) in methanol (200 mL) was added sodium acetate (6.33 g, 77.2 mmol, 4 equivalents) and hydroxylamine hydrochloride (4.02 g, 57.9 mmol, 3 equivalents). After stirring one hour, 1N sodium hydroxide (100 mL) was added and the mixture extracted with methylene chloride (2 X 100 mL, 1 X 50 mL). The combined organics were washed with brine (100 mL), dried over MgSO,, filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (50% ethyl acetate in hexane) to afford the desired title compound as a yellow foam (8.64 g, 97.9%): 'H NMR

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(t, J = 12.6 Hz, 1 H), 2.10 (t, J = 11.5 Hz, 1H), 2.79 1H), 6.19 (8, 1H), 6.54 (dd, J = 8.9, 1.9 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.82 (8, 1H), 6.86 (d, J = 7.2 Hz, (CD,OD) 8 0.86-0.97 (m, 6H), 1.07-1.52 (m, 10H), 1.76 (8, 6H), 3.05-3.18 (qu, 2H), 4.10 (8, 1H), 5.22 (8, 1H), 7.14 (t, J a 7.8 Hz, 1H), 7.73 (d, J = 8.9 Hz,

BIOLOGICAL ASSAYS

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essentially using a procedure recognized to show the invention is shown by the following assays. These assays are performed in vitro and in animal models The utility of the compounds of the present utility of the present invention.

In Vitro Ansay of compounds that inhibit IBAT-modiated uptake of [14C]-Taurocholate (TC) in H14 Cello

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Baby hamster kidney cells (BHK) transfected with 60,000 cells/well in 96 well Top-Count tissue culture 30,000 cells/well for assays run within 48 hours, and plates for assays run within in 24 hours of seeding, 10,000 cells/well for assays run within 72 hours. the cDNA of human IBAT (H14 cells) are seeded at

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On the day of assay, the cell monolayer is gently 0.2% (w/v) (FAF)BSA. The wells are then gently washed culture plates are incubated 2 hours at 37°C prior to (w/v) fatty acid free bovine serum albumin- (PAF) BSA) To each well 50 µl of a two-fold concentrate of test compound in assay buffer is added along with 50 µl of Dulbecco's phosphate-buffered saline (PBS) containing Modified Eagle's medium with 4.5 g/L glucose + 0.2% concentration of 3 μM [14C]-taurocholate). The cell washed once with 100 µl assay buffer (Dulbecco's gently washing each well twice with 100 μ 1 4° C $6 \, \mu M \, [^{14}C]$ -taurocholate in assay buffer (final

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amount of radioactivity in each well on a Packard Toponce with 100 µl 4° C PBS without (FAF) BSA. To each added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the 200 µl of liquid scintillation counting fluid is Count instrument,

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In Vitro Assay of compounds that inhibit uptake of ['C]-Alanine

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exception that labeled alanine is substituted for the identical fashion to the taurocholate assay, with the The alanine uptake assay is performed in an labeled taurocholate,

In Vivo Assay of compounds that inhibit Rat Ilon uptake of ['C]-Taurocholate into Bilo

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(See" Metabolism of 3α , 7β -dihydroxy- 7α -methyl- 5β -Biophysica Acta 833 (1985) 196-202 by Une et al.) cholanoic acid and 3lpha, 7eta-dihydroxy-7lpha-methyl-5etacholanoic acid in hamsters" in Biochimica et

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this same junction (utilizing a 8 cm length of 11eum). min with warm PBS at 0.25 ml/min. Temperature of the Intestine and the cecum. A slit is cut at 4 cm from canulae (1/8" luer lock, tapered female adapter) is aegment. The distal opening is cannulated with a 20 20 ml of warm Dulbecco's phosphate buffered saline, gut segment is monitored continuously. At the start with inactin @100 mg/kg. Bile ducts are cannulated peristaltic pump and the intestine is washed for 20 Male wistar rats (200-300 g) are anesthetized intestine is exposed and laid out on a gauze pad. cm length of silicone tubing (0.02" I.D. imes 0.037" inserted at 12 cm from the junction of the small The proximal cannulae is hooked up to a pH 6.5 (PBS) is used to flush out the intestine with a 10" length of PB10 tubing. The small

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control sample. is performed as above that typically contains the by 21 min of wash out) and bile sampled every 3 min administered as well (21 min administration followed described above but this with test compound being 0.25 ml/min. A second perfusion is initiated as the loop is washed out for 21 min with warm PBS at 20 ml of warm PBS (using a 30 ml syringe), and then of sample infusion, the ileal loop is washed out with samples fractions are collected every 3 minute for the infused at a rate of 0.25 ml/min for 21 min. Bile bile sample collection is begun. Control sample is is loaded into the gut segment with a 3 ml syringe and taurocholate @ 0.05 mi/ml with 5 mM cold taurocholate) of the experiment, 2.0 ml of control sample ([14C]for the first 27 min. first 27 minutes of the procedure. After the 21 min If necessary, a third perfusion

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Measurement of Hepatic Cholesterol Concentration (HEPATIC CHOL)

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Liver tissue was weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant was separated and dried under nitrogen. The residue was dissolved in isopropanol and the cholesterol content was measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., et al. (1974) Clin. Chem. 20, 470.

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Measurement of Hepatic HMG Coh-Reductase Activity (HMG COh)

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Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for HMG COA reductase activity by incubating for 60

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minutes at 37° C in the presence of 'C-HMG-COA (Dupont-NEN). The reaction was stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant was separated, by thin-layer chromatography, and the spot corresponding to the enzyme product was scraped off the plate, extracted and radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) J. Lipid Res. 31, 2159).

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Determination of Serum Cholesterol (SER.CHOL, NDL-CHOL, TGI and VLDL + LDL)

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Total serum cholesterol (SER.CHOL) was measured enzymatically using a commercial kit from Wako Pine Chemicals (Richmond, VA); Cholesterol C11, Catalog No 276-64909. HDL cholesterol (HDL-CHOL) was assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) were assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations were calculated as the difference between total and HDL cholesterol.

Memsurement of Hepatic Cholesterol 7-a-Hydroxylase Activity (7a-Ohase)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for cholesterol 7- α -hydroxylass activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent was evaporated and the residue was dissolved in acetonitrile/ methanol. The enzymatic product was

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separated by injecting an aliquot of the extract onto a C., reversed phase HPLC column and quantitating the (Reference: Horton, J. D., et al. (1994) J. Clin. eluted material using UV detection at 240nm. Invest. 93, 2084).

Rat Gavage Assay

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Male Wister rats (275-300g) are administered IBAT of the increase in fecal bile acid (FBA) concentration Total fecal samples are collected during the final 48 rehicle (0.2% Tween 80 in water) is administered once in a final volume of 2 mL per kilogram of body weight below. Compound efficacy is determined by comparison in treated rats to the mean FBA concentration of rats a day (9:00-10:0 a.m.) for 4 days at varying dosages Inhibitors using an oral gavage procedure. Drug or hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described in the vehicle group.

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Measurement of Pecal Bile Acid Concentration (FBA)

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hamsters was collected for 24 or 48 hours, dried under Approximately 0.1 gram was weighed out and extracted separation and drying, the residue was dissolved in into an organic solvent (butanol/water). Following measured enzymatically using the 3α -hydroxysteroid reduce NAD. (Reference: Mashige, F., et al. (1981) steroid dehydrogenase reaction with bile acids to Total fecal output from individually housed methanol and the amount of bile acid present was setream of nitrogen, pulverized and weighed. Clin. Chem. 27, 1352).

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(H) taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

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Rabbit Ileal brush border membranes were prepared

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μl solution containing 2μM [³H]-taurocholate(0.75 μC1), Biochimica Biophysica Acta, 554, 259). The method for measuring taurocholate was essentially as described by Kramer et al. (Reference: (1992) Biochimica Biophysica instead of 100 μ l. Briefly, at room temperature a 190 membrane vesicles (60-120 µg protein). The incubation vortexing and the reaction was stopped by the addition nylon filter (0.2 µm pore) and an additional 5 ml wash from frozen ileal mucosa by the calcium precipitation of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM method describe by Malathi et al. (Reference: (1979) 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was Acta, 1111, 93) except the assay volume was 200 μl KCl) followed immediately by filtration through a was initiated by the addition of the BBMV while incubated for 5 sec with 10 µl of brush border with stop buffer.

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Acyl-CoA; cholesterol Acyl Transferage (ACAT)

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chloroform phase was taken to dryness and then spotted Hamster liver and rat intestinal microsomes were Reference: (1980) J. Biol. Chem. 255, 9098) and used as a source of ACAT enzyme. The assay consisted of a buffer containing 0.25 % BSA and 200 µg of microsomal oleoyl-CoA. The reaction went for 5 min at 37° C and protein. The assay was initiated by the addition of 2.0 ml incubation containing 24 μM Oleoyl-CoA (0.05 squeous phases of the extraction were separated by μCi) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 chloroform/ methanol (2:1). To the extraction was methanol to act as a carrier and the organic and added 125 µg of cholesterol oleate in chloroform on a silica gel 60 TLC plate and developed in prepared from tissue as described previously was terminated by the addition of 8.0 ml of centrifugation after thorough vortexing.

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hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard instaimager.

TABLE 11
Rat Gavage Assay Data for Some Additional Compounds
of the Present Invention

1408	1408	1407	1407	1406	1404	1403	1402	1402	Compound of Example No.
37	29	33	3 2	32	28	30	30	28	Study No.
.4 .08 .016	2 .4 .08 .016	.4 .08 .016	2 .4 .08	2 .4 .08 .016	. 2 . 04	.4 .08 .016	.4 .08 .016	.2 .04	Dose (mg/kg/day)
26.2 45.2 26.3 6.6	41.2 16.8 -3.3	35 12.7 04 -4.5	51.9 30.1 27.5 6.4	47.8 31.6 12.8 -8.5	93.7 59.1 33.5	41.6 35.2 11.9 3	50.3 40.9 48.5 22.9	58.2 1.3 0.3	Delta (micromoles fecal bile acid per day)

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1419	1418	1417	1416	1415	1415	1414	1414	1413	1411	1410	1410	1409	1409
31	29	31	29	37	22 8	31	27	26	34	35	33	41	ພ
.4	.4 .08 .016	.4 .08 .016	.4 .08 .016	.4 .08 .016	.2 .04	.4 .08 .016	.22	.2 .04	2 .4 .08 .016	2 .4 .08 .016	32.4 34.3 27.9 9.3	.4 .08 .016	.4 .08
28.5 13.9	20.3 29.5 -4.6 -10	51.4 42 39.6 29.3	46.1 21.9 25 -7.8	48.9 25.7 27.1 12.7	59.9 48.1 23.9	41.5 33.7 29 3.8	45.2 39.5 14.3	52.3 42.4 19	63.4 54.1 33 22.3	26.2 36.5 18.5 20.4		44.2 35.9 14.5 11	19.2 28.7 14.1

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26 1.1	34.5 24.9 18.7	9.2 47.1 31.1 35.5	51.2 50.4 20.7		36.2	66.5 47.4 26.5
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•	41	42	30	32	28	24
	1429	1429	1430	1431	1432	1433

conditions of this invention for those used in the specifically described reactants and/or operating The examples herein can be repeated with similar success by substituting the generically or preceding examples.

and all such modifications and equivalents as would be Such variations are not to be regarded as a departure obvious to one skilled in the art are intended to be The invention being thus described, it is from the spirit and scope of the present invention, apparent that the same can be varied in many ways. included within the scope of the following claims.

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A compound of formula (I):

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wherein:

n is an integer from 0 to 2; q is an integer from 1 to 4;

alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylthio, (polyalkyl)aryl, and cycloalkyl, \mathbb{R}^1 and \mathbb{R}^2 are independently selected from the group

halogen, oxo, and CONR⁹R¹⁰, S'R'R''A'. P+R9R10R11A-, S(O)R9, SO2R9, SO3R9, CO2R9, CN the group consisting of OR9, NR9R10, N+R9R10RWA-, SR9, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino substituted with one or more substituents selected from wherein alkyl, alkenyl, alkynyl, haloalkyl,

s, so, so₂, s⁺R⁹A⁻, p⁺R⁹R¹⁰A⁻, or phenylene, have one or more carbons replaced by 0, NR9, N+R9R10Aalkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy,

> alkylammoniumalkyl; or carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino arylalkyl, carboxyalkyl, carboxyheteroaryl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, from the group consisting of H, alkyl, alkenyl, alkynyl, heteroarylalkyl, heterocyclylalkyl, and wherein \mathbb{R}^9 , \mathbb{R}^{10} , and \mathbb{R}^W are independently selected

they are attached form C3-C3, cycloalkyl; \mathbb{R}^1 and \mathbb{R}^2 taken together with the carbon to which

wherein R' and R' are as defined above; or heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹ consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl \mathbb{R}^3 and \mathbb{R}^4 are independently selected from the group

-NR7, or -CR11R12, R3 and R4 together form =0, =NOR11, =S, =NNR11R12

NH, and SH, or or, NR9R10, SR9, S(0)R9, SO2R9, SO3R9, CO2R9, CN, defined above, provided that both R³ and R⁴ cannot be OH, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, the group consisting of H, alkyl, alkenyl, alkynyl, aryl, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, wherein R^{11} and R^{12} are independently selected from

atom to which they are attached form a cyclic ring; \mathbb{R}^{11} and \mathbb{R}^{12} together with the nitrogen or carbon

 R^5 is aryl substituted with one or more OR^{13a}

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl alkylheterocyclylalkyl, heterocyclylalkyl, of alkylarylalkyl, alkylheteroarylalkyl, wherein \mathbb{R}^{13a} is selected from the group consisting

amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, $^{N^+}R^9R^{11}R^{12}A^-$, $^{SR}^9$, S (0) $^{R}^9$, S 02 $^{R}^9$, S 03 R , S 00, S 00, groups selected from the group consisting of hydroxy, R^{13a} is optionally substituted with one or more quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, OR⁹, NR⁹R¹⁰, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, heteroaryl, sulfoalkyl, quaternary heterocycle, P*R9R10R11A-, S*R9R10A-, and C(0) OM,

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R9 and M; and

alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and ${\tt R}^{\sf G}$ is selected from the group consisting of H,

 ${
m SO_2OM},\ {
m SO_2NR}^{13}{
m R}^{14},\ {
m C(0)\,NR}^{13}{
m R}^{14},\ {
m C(0)\,OM},\ {
m COR}^{13},\ {
m NR}^{13}{
m C(0)\,R}^{14},$ arylalkyl, quaternary heterocycle, quaternary heteroaryl, substituent groups independently selected from the group wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, NR"C(0) NR"R", NR"CO3R", OC(0) R", OC(0) NR"R", NR"SOR", polyether, aryl, haloalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heterocycle, and quaternary halogen, oxo, OR^{13} , $\mathrm{NR}^{13}\mathrm{R}^{14}$, SR^{13} , $\mathrm{S}(\mathrm{O})\mathrm{R}^{13}$, $\mathrm{SO}_2\mathrm{R}^{13}$, ${
m SO_3R^{13}}$, ${
m NR^{13}OR^{14}}$, ${
m NR^{13}NR^{14}R^{15}}$, ${
m NO_2}$, ${
m CO_2R^{13}}$, ${
m CN}$, ${
m OM}$, consisting of alkyl, alkenyl, alkynyl, polyalkyl, heteroaryl can be substituted with one or more NR¹³SO₂R¹⁴, NR¹³SONR¹⁴R¹³, NR¹³SO₂NR¹⁴R¹⁵, P(O)R¹³R¹⁴,

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p+R13R14R15A-, P(OR13)OR14, S+R13R14A-, and N+R9R11R12A-,

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

S(0)R7, SO2R7, SO3R7, CO2R7, CN, OXO, CONR7R8, N*R7R8R9A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, further substituted with one or more substituent groups selected from the group consisting of OR7, NR7R8, SR7, aryl, haloalkyl, cycloalkyl, and heterocycle can be P(0)R7R8, P+R7R8R9A-, and P(0) (OR7)OR8, and

NR7, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-; PR⁷, P(O)R⁷, P⁺R⁷R⁹A-, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, can optionally have one or more carbons replaced by 0, selected from the group consisting of hydrogen, alkyl, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently wherein said alkyl, alkenyl, alkynyl, polyalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkylarylalkyl, alkylheteroarylalkyl,

carbons replaced by O, NR', N'R'R'10A-, S, SO, SO2, S'R'A', heterocycle, and polyalkyl optionally have one or more PR⁹, P⁺R⁹R¹⁰A-, P(O)R*, phenylene, carbohydrate, amino wherein alkyl, alkenyl, alkynyl, arylalkyl, acid, peptide, or polypeptide, and

 R^{13} , R^{14} , and R^{15} are optionally substituted with

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SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO2OM, guanidinyl, ox9, NR9R10, N+R9R11R12A-, SR9, S(O)R9, heterocyclylalkyl, quaternary heteroarylalkyl, C(0) OM, SO2NR 9R 10, PO (OR 16) OR 17, P + R 9R 10R 11A-, S + R 9R 10A-, and heterocycle, quaternary heteroaryl, quaternary heterocycle, heteroaryl, sulfoalkyl, quaternary one or more groups selected from the group consisting hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, e

the substituents constituting R^9 and M_i or wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected from

quaternary salts; or selected from the group consisting of oxo, carboxy and that is optionally substituted with one or more radicals they are attached form a mono- or polycyclic heterocycle R" and R", together with the nitrogen atom to which

which they are attached, form a cyclic ring; and \mathbb{R}^{14} and \mathbb{R}^{15} , together with the nitrogen atom to

heterocyclylalkyl, and alkylammoniumalkyl; and carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyalkyl, carboxyhateroaryl, carboxyhaterocycle, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, R is selected from the group consisting of alkyl,

consisting of hydrogen and alkyl; and $^{\mathsf{R}^{\mathsf{7}}}$ and $^{\mathsf{8}}$ are independently selected from the group

group consisting of H, alkyl, alkenyl, alkynyl, quaternary heterocycle, quaternary heteroaryl, OR13 cycloalkyl, heterocycle, heteroaryl, polyether, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, one or more $R^{\mathbf{X}}$ are independently selected from the

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 $p^{+}R^{9}R^{1}R^{1}A^{-}$, amino acid, peptide, polypeptide, and carbohydrate, COR¹³, OR¹⁸, S(0)_{INK}18, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A $502NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, $C(0)NR^{13}R^{14}$, NR14C(0)R13, C(0)OM ${\rm NR}^{13}{\rm OR}^{14}$, ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$, ${\rm NO}_2$, ${\rm CO}_2{\rm R}^{13}$, ${\rm CN}$, ${\rm OM}$, ${\rm SO}_2{\rm OM}$, NR13R14, SR13, S(0)R13, S(0)2R13, SO3R13, S+R13R14A-,

 $P^{+}R^{9}R^{11}R^{12}A^{-}$, $S^{+}R^{9}R^{10}A^{-}$, or C(0)0M, and $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $S0_{2}R^{9}$, $S0_{3}R^{9}$, OXO, $CO_{2}R^{9}$, CN, halogen, $conr^9 r^{10}$, $so_2 om$, $so_2 ur^9 r^{10}$, $ro(or^{16}) or^{17}$, heteroaryl can be further substituted with oR⁹, NR⁹R¹⁰ polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

heteroaryl, alkyl, acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein \mathbb{R}^{18} is selected from the group consisting of

SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO3R9 SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM, and quaternary heteroaryl optionally are substituted with consisting of OR 9 , NR 9 R 10 , N 4 R 9 R 11 R 12 A $^-$, SR 9 , S(O)R 9 , one or more substituents selected from the group heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl,

peptide, polypeptide, carbohydrate, polyether, or pR^{13} , $P(0)R^{13}$, $p^{+}R^{13}R^{14}A^{-}$, phenylene, amino acid, replaced by 0, NR^{13} , $N^{+}R^{13}R^{14}A^{-}$, S, SO, SO₂, $S^{+}R^{13}A^{-}$, wherein in $R^{\mathbf{x}}$, one or more carbons are optionally

wherein in said polyalkyl, phenylene, amino acid,

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carbons are optionally replaced by 0, NR⁹, N*R⁹R¹⁰A⁻, S, peptide, polypeptide, and carbohydrate, one or more so, so₂, s⁺R³A-, PR⁹, P⁺R⁹R¹⁰A-, or P(0)R⁹;

alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, ∞ o, $0\mathrm{R}^{13}$ heteroaryl are optionally substituted with one or more C(0) NR¹³R¹⁴, C(0) OM, COR¹³, P(0) R¹³R¹⁴, P*R¹³R¹⁴R¹⁵A⁻, a pharmaceutically acceptable salt, solvate, or NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, groups selected from the group consisting of alkyl, wherein quaternary heterocycle and quaternary NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, P(OR13)OR14, 8+R13R14A, and N*R9R11R12A, or

2. A compound of claim 1 wherein:

prodrug thereof.

R' is phenyl substituted with OR¹³⁴;

consisting of alkylarylalkyl, alkylheteroarylalkyl, R^{11} is independently selected from the group carboxyalkylaminocarbonylalkyl; and alkylheterocyclylalkyl, and

R¹¹⁸ is optionally substituted with one or more groups selected from the group consisting of carboxy, quaternary heterocycle, quaternary heteroaryl, and NR'R".

- 3. A compound of claim 1 wherein n is 1 or 2.
- 4. A compound of claim 1 wherein R' and R' are independently selected from the group consisting of hydrogen and alkyl.

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5. A compound of claim 1 wherein R' and R' are hydrogen. 6. A compound of claim 1 wherein R' and R' are independently selected from the group consisting of hydrogen and OR'. 7. A compound of claim 1 wherein R' is hydrogen and R' is hydroxy. 8. A compound of claim 1 wherein one or more R" are independently selected from the group consisting of OR" and NR¹³R¹⁴. 9. A compound of claim 1 wherein one or more R are independently selected from methoxy and dimethylamino.

10. A compound of claim 1 wherein R' and R' are independently selected from the group consisting of hydrogen and alkyl.

independently selected from the group consisting alkyl. 11. A compound of claim 1 wherein R' and R' are

12. A compound of claim 1 wherein R1 and R2 are the same alkyl. 13. A compound of claim 1 wherein R' and R' are each

14. A compound of claim 1 wherein n is 1 or 2;

R' and R' are n-butyl;

R' and R' are hydrogen;

R is hydroxy;

15. A compound of claim 1 having the structural

16. A compound of claim 1 having the structural

formula: 17. A compound of claim 1 having the structural

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18. A compound of claim 1 having the structural

19. A compound of claim 1 having the structural

20. A compound of claim 1 having the structural

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21. A compound selected from the group consisting of:

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Bu

; and

22. A compound of formula (I):

$$(R^{3})_{q} = \begin{bmatrix} 0 \\ 1 \\ 1 \\ 2 \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \\ 2 \\ 4 \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \\ 3 \end{bmatrix}$$

$$R^{2}$$

$$R^{3}$$

$$R^{4}$$

$$R^{2}$$

$$R^{3}$$

$$R^{4}$$

$$R^{2}$$

$$R^{3}$$

$$R^{4}$$

$$R^{3}$$

$$R^{4}$$

$$R^{2}$$

$$R^{4}$$

$$R^{5}$$

$$R^{4}$$

$$R^{5}$$

$$R^{4}$$

$$R^{5}$$

wherein:

q is an integer from 1 to 4, n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaxyl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹Rl⁰, N*R⁹Rl⁰R^MA⁻, SR⁹,

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S'R'R''A. P⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A, p⁺R⁹R¹⁰A, or phenylene,

wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

 $\rm R^{1}$ and $\rm R^{2}$ taken together with the carbon to which they are attached form C,-C, cycloalkyl;

R³ and R⁴ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, and SO₃R⁹, wherein R⁹ and R¹⁹ are as defined above; or

 $\rm R^3$ and $\rm R^4$ together form =0, =NOR 11 , =S, =NNR $^{11}\rm R^{12}$,=NR 9 , or =CR $^{11}\rm R^{12}$,

wherein R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alknyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CO₃R⁹, NR⁹R¹⁰, SR⁹, SO₃R⁹, Wherein R⁹ and R¹⁰ are as defined above, provided that both R³ and R⁴ cannot be OH, NH, and SH, or

 ${
m R}^{11}$ and ${
m R}^{12}$ together with the nitrogen or carbon

atom to which they are attached form a cyclic ring \mathbb{R}^5 is anyl substituted with one or more \mathbb{QR}^{13b}

of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, \mathbb{R}^{13b} is substituted with one or more groups selected wherein R^{13b} is selected from the group consisting

quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle heteroarylalkyl, or guanidinyl, and heteroaryl, quaternary heterocyclylalkyl, quaternary from the group consisting of carboxyalkyl, heterocycle, R⁶ is selected from the group consisting of H,

NR"SO,R", NR"SONR"R", NR"SO,NR"R", P(0)R13R14 NR11C(0)NR14R11, NR11CO,R14, OC(0)R11, OC(0)NR11R14, NR11SOR14, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13} , $NR^{12}C(O)R^{14}$ SO3R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO2, CO2R¹³, CN, OM, halogen, oxo, OR13, NR13R14, SR13, S(O)R13, SO2R13, arylalkyl, quaternary heterocycle, quaternary heteroaryl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heteroaryl can be substituted with one or more p+R13R14R15A-, P(OR13)OR14, S+R13R14A-, and N+R9R11R12Aheterocycle, quaternary heterocycle, and quaternary wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

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pharmaceutically acceptable cation, A is a pharmaceutically acceptable anion and M is a

 $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and arylalkyl, quaternary heterocycle, quaternary heteroaryl , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle $s(0)R^7$, so_2R^7 , so_3R^7 , co_2R^7 , cn, oxo, $conR^7R^8$, $n^+R^7R^8R^9A$. selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups said alkyl, alkenyl, alkynyl, polyalkyl, polyether,

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle alkylarylalkyl, alkylheteroarylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl selected from the group consisting of hydrogen, alkyl, or phenylene, and \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are independently NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R7, P+R7R8A-, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle heteroaryl, quaternary heterocycle, quaternary can optionally have one or more carbons replaced by O, wherein said alkyl, alkenyl, alkynyl, polyalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl,

acid, peptide, or polypeptide, and pR^9 , $p^+R^9R^{10}A^-$, $P(0)R^8$, phenylene, carbohydrate, amino carbons replaced by 0, NR, N+R9R10A-, S, SO, SO2, S+R9A; heterocycle, and polyalkyl optionally have one or more

one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are optionally substituted with

heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, OR, NR9R10, N*R9R1R1ZA-, SR9, S(O)R9, SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO2OM, SO2NR9R10, PO(OR16)OR17, P*R9R10R1A-, S*R9R10A-, and COOON.

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R¹¹ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 R^{14} and $R^{15},$ together with the nitrogen atom to which they are attached, form a cyclic ring, and

R. 18 selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, arylalkyl, carboxyheteroaryl, carboxyheteroaryl, carboxyheteroaryl, carboxyheteroaryl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $\rm R^7$ and $\rm R^8$ are independently selected from the group consisting of hydrogen and alkyl, and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heteroaryl, oR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, S(0)₂R¹³, SO₃R¹³, S¹³R¹³R¹⁴A₋, NR¹³OR¹⁴, NR¹³OR¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM,

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SO2NR¹³R¹⁴, NR'C(O)R'', C(O)NR¹³R¹⁴, NR14C(O)R13, C(O)OM, COR¹³, OR¹⁸, S(O)_DNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻, p⁺R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N[‡]R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂ONF⁹R¹⁰, PO(OR¹¹)OR¹⁷, p[‡]R⁹R¹¹R¹²A⁻, S[‡]R⁹R¹⁰A⁻, or C(O)OM, and

wherein \mathbb{R}^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR, NR9R10, N*R9R11R12A, SR9, S(O)R9, SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO3R9, SO2NR9R10, PO(OR16)OR17, and C(O)OM,

wherein in R^X, one or more carbons are optionally replaced by 0, NR¹³, N⁺R¹³R¹⁴A⁻, S, SO, SO₂, S⁺R¹³A⁻, PR¹³, p (0)R¹³, p+R¹³R¹⁴A⁻, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR 9 , N $^+$ R 9 R 1 O $^+$. S,

so, so₂, s⁺R⁹A-, pR⁹, p⁺R⁹R¹⁰A-, or P(0)R⁹;

groups selected from the group consisting of alkyl, P(OR13)OR14, S+R13R14A, and N+R9R11R12A, or $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $P(0)R^{13}R^{14}$, $P^{+}R^{13}R^{14}R^{15}A^{-}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, NR13R14, SR13, S(0)R13, SO2R13, SO3R13, NR13OR14, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, prodrug thereof. heteroaryl are optionally substituted with one or more a pharmaceutically acceptable salt, solvate, or wherein quaternary heterocycle and quaternary

A compound of claim 22 wherein:

consisting of alkyl, quaternary heteroarylalkyl, and quaternary heterocyclylalkyl; and R^{136} is independently selected from the group R' is phenyl substituted with OR115;

guanidinyl. from the group consisting of heterocycle, heteroaryl, and R is substituted with one or more groups selected

- A compound of claim 22 wherein n is 1 or 2.
- hydrogen and alkyl. independently selected from the group consisting of A compound of claim 22 wherein R' and R' are
- A compound of claim 22 wherein R' and R' are
- independently selected from the group consisting of 27. A compound of claim 22 wherein R' and R' are

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hydrogen and OR'

- R' is hydroxy. 28. A compound of claim 22 wherein R' is hydrogen and
- and NR"R". independently selected from the group consisting of OR13 29. A compound of claim 22 wherein one or more R* are
- independently selected from methoxy and dimethylamino. 30. A compound of claim 22 wherein one or more R are
- hydrogen and alkyl. independently selected from the group consisting of 31. A compound of claim 22 wherein R' and R' are
- independently selected from the group consisting alkyl. 32. A compound of claim 22 wherein R' and R' are
- 33. A compound of claim 22 wherein R' and R' are the
- n-butyl. 34. A compound of claim 22 wherein R' and R' are each
- A compound of claim 22 wherein
- n is 1 or 2;
- R' and R' are n-butyl;
- R' and R' are hydrogen;
- R' is hydroxy;
- R' and R' are hydrogen; and
- and dimethylamino. one or more R* are independently selected from methoxy

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36. A compound of claim 22 having the structural formula:

A compound of claim 22 having the structural formula:

. A compound of formula (I):

 $\widehat{\Xi}$

herein.

q is an integer from 1 to 4,

n is an integer from 0 to 2;

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R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkylaryl, dialkylamino, alkylatyl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹Rl⁰, N⁺R⁹Rl⁰R⁴-, SR⁹, S'R⁴R⁴A. P⁸R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A, P⁺R⁹R¹⁰A-, or phenylene,

wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyheterocycle, carboalkoxyalkyl, and heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl, or

 $\rm R^1$ and $\rm R^2$ taken together with the carbon to which they are attached form C,-C, cycloalky1,

 $\rm R^3$ and $\rm R^4$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR 9 , NR $^9R^{10}$, SR 9 , S(O)R 9 , SO2R 9 , wherein R 8 and R 19 are as defined above, or

 $\rm R^3$ and $\rm R^4$ together form =0, =NOR 11 , =5, =NNR $^{11}\rm R^{12}$,=NR 9 , or =CR $^{11}\rm R^{12}$,

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OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, defined above, provided that both \mathbb{R}^3 and \mathbb{R}^4 cannot be OH halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, the group consisting of H, alkyl, alkenyl, alkynyl, aryl, NH2, and SH, or wherein \mathbf{R}^{11} and \mathbf{R}^{12} are independently selected from

atom to which they are attached form a cyclic ring; ${f R}^{11}$ and ${f R}^{12}$ together with the nitrogen or carbon

R⁵ is aryl substituted with one or more OR 13b

carboxyalkylaminocarbonylalkyl, alkoxyalkyl, alkylammoniumalkyl, and quaternary heterocyclylalkyl, quaternary heteroarylalkyl heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle, of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, wherein R^{13b} is selected from the group consisting

SO2NR9aR10, p+R9aR10R11A-, and S+R9aR10A-, from the group consisting of OR 9a, NR 9aR 10, N+R 9aR 11R 12A- SR^{9a} , $S(0)R^{9a}$, SO_2R^{9a} , SO_3R^{9a} , CO_2R^{9a} , $CONR^{9a}R^{10}$ \mathbb{R}^{13b} is substituted with one or more groups selected

and M is a pharmaceutically acceptable cation, and wherein A is an pharmaceutically acceptable anion

carboalkoxyalkyl, carboxyalkylamino, and carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboxyalkylaminoalkyl; wherein R^{9a} is selected from the group consisting of

> quaternary heterocycle, OR^{30} , SR^9 , $S(0)R^9$, SO_2R^9 , and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, R⁶ is selected from the group consisting of H,

 $p^{+}R^{13}R^{14}R^{15}A^{-}$, $P(OR^{13})OR^{14}$, $S^{+}R^{13}R^{14}A^{-}$, and $N^{+}R^{9}R^{11}R^{12}A^{-}$ NR11503R14, NR1150NR11R15, NR11503NR11R15, P(0)R13R14 NR12C(0)NR14R15, NR12CO2R14, OC(0)R13, OC(0)NR12R14, NR13SOR14 SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $NR^{13}C(0)R^{14}$ $503R^{13}$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heteroaryl can be substituted with one or more heterocycle, quaternary heterocycle, and quaternary wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

pharmaceutically acceptable cation, A is a pharmaceutically acceptable anion and M is

 $P(0)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(0)(0R^7)OR^8$, and $s(0)R^{7}$, $so_{2}R^{7}$, $so_{3}R^{7}$, $co_{2}R^{7}$, cn, oxo, $conR^{7}R^{8}$, $n^{+}R^{7}R^{8}R^{9}A$ aryl, haloalkyl, cycloalkyl, and heterocycle can be arylalkyl, quaternary heterocycle, quaternary heteroaryl , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , further substituted with one or more substituent groups said alkyl, alkenyl, alkynyl, polyalkyl, polyether

polyether, aryl, haloalkyl, cycloalkyl, and heterocycle wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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can optionally have one or more carbons replaced by 0, NR 7 , N 4 R 7 R 8 A-, S, SO, SO₂, S 4 R 7 A-, PR 7 , P(O)R 7 , P 4 R 7 R 8 A-, or phenylene, and R 13 , R 14 , and R 15 are independently selected from the group consisting of hydrogen, alkyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylheteroarylalkyl, alkylheteroarylalkyl, alkylheteroarylalkyl, alkylheterogycle,

heteroaryl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, heterocarylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by 0, NR', N*R*R*10*A-, 5, SO, SO2, S*R*A,

PR⁹, p⁺R⁹R¹⁰A₋, P(0)R⁴, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and R¹³, R¹⁴, and R¹⁵ are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, so₂ox, Co₂R⁹, Cx, halogen, CONR⁹R¹⁰, So₂Ox, So₂NR⁹, po(OR¹⁶)OR¹⁷, p⁺R⁹R¹⁰R¹¹A₋, s⁺R⁹R¹⁰A₋, and COONR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, p⁺R⁹R¹⁰R¹¹A₋, s⁺R⁹R¹⁰A₋, and

wherein $\rm R^{16}$ and $\rm R^{17}$ are independently selected from the substituents constituting $\rm R^9$ and M, or

 R^{11} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals

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selected from the group consisting of oxo, carboxy and quaternary salts; or

 R^{14} and $R^{15},$ together with the nitrogen atom to which they are attached, form a cyclic ring, and

R** is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $\rm R^7$ and $\rm R^8$ are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, oR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)2R¹³, SO₂R¹³, S²R¹³R¹⁴, NR¹³CO²R¹³, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁶C(O)R¹³, C(O)NR¹³R¹⁴, NR¹⁶C(O)R¹³, C(O)R¹³R¹⁸, NR¹⁸OR¹⁴, N²R⁹R¹¹R¹²A⁻, p²R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹¹)OR¹⁷, p⁺R⁹R¹¹R¹²A⁻, S⁺R⁹R¹⁰A⁻, or C(O)OM, and

 so_2om , $so_2nR^9R^{10}$, $po(oR^{16})oR^{17}$, and c(0)oM, SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO3R9 consisting of OR9, NR9R10, N+R9R11R12A-, SR9, S(0)R9, one or more substituents selected from the group and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

PR13, P(0)R13, P+R13R14A-, phenylene, amino acid, polyalkyl, peptide, polypeptide, carbohydrate, polyether, or replaced by 0, NR¹³, N⁺R¹³R¹⁴A-, S, SO, SO₂, S⁺R¹³A⁻, wherein in Rx, one or more carbons are optionally

so, so₂, s⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(0)R⁹; carbons are optionally replaced by 0, NR^9 , $N^+R^9R^{10}A^-$, s, peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid,

P(OR13) OR14, S+R13R14A-, and N+R9R11R12A-, or $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $P(0)R^{13}R^{14}$, $P^{\dagger}R^{13}R^{14}R^{15}A^{-}$, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴ NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴ cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³ alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

prodrug thereof. a pharmaceutically acceptable salt, solvate, or

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39. A compound of claim 38 wherein:

R* is phenyl substituted with OR111;

and alkoxyalkyl; and R116 is selected from the group consisting of alkyl

from the group consisting of OR" and NR"R"; and R115 is substituted with one or more groups selected

carboxyalkyl, carboxyheteroaryl, and carboxyheterocycle; R** is selected from the group consisting ef.

R10 is carboxyalkyl.

- 40. A compound of claim 38 wherein n is 1 or 2.
- hydrogen and alkyl. independently selected from the group consisting of 41. A compound of claim 38 wherein R' and R' are
- hydrogen. 42. A compound of claim 38 wherein R' and R' are
- hydrogen and OR'. independently selected from the group consisting of 43. A compound of claim 38 wherein R' and R' are
- R' is hydroxy. 44. A compound of claim 38 wherein R is hydrogen and
- and NR11R14. independently selected from the group consisting of OR11 45. A compound of claim 38 wherein one or more R*
- independently selected from methoxy and dimethylamino. 46. A compound of claim 38 wherein one or more R*

47. A compound of claim 38 wherein R' and R' are independently selected from the group consisting of hydrogen and alkyl.

independently selected from the group consisting alkyl. 48. A compound of claim 38 wherein R1 and R2 are

50. A compound of claim 38 wherein R¹ and R² are each 49. A compound of claim 38 wherein R1 and R2 are the same alkyl.

51. A compound of claim 38 wherein

n-butyl.

n is 1 or 2;

R' and R' are n-butyl; R' and R' are hydrogen;

R* is hydroxy;

one or more R' are independently selected from methoxy R' and R' are hydrogen; and and dimethylamino.

52. A compound of claim 38 having the structural formula:

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53. A compound of claim 38 having the structural formula:

54. A compound of claim 38 having the structural

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A compound of formula (I):

ან :

n is an integer from 0 to 2; q is an integer from 1 to 4;

alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylthio, (polyalkyl)aryl, and cycloalkyl, R^1 and R^2 are independently selected from the group

halogen, oxo, and CONR⁹R¹⁰, $s^{*}R^{*}R^{*0}A^{*}$. $p^{+}R^{9}R^{10}R^{11}A^{-}$, $s(0)R^{9}$, $so_{2}R^{9}$, $so_{3}R^{9}$, $co_{2}R^{9}$, $co_{3}R^{9}$ the group consisting of OR9, NR9R10, N+R9R10RWA-, SR9, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, wherein alkyl, alkenyl, alkynyl, haloalkyl,

s, so, so₂, s⁺R⁹A⁻, p⁺R⁹R¹⁰A⁻, or phenylene, have one or more carbons replaced by 0, NR⁹, N[†]R⁹R¹⁰Aalkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy

cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, from the group consisting of H, alkyl, alkenyl, alkynyl arylalkyl, carboxyalkyl, carboxyheteroaryl, wherein R^9 , R^{10} , and R^W are independently selected

alkylammoniumalkyl; or heteroarylalkyl, heterocyclylalkyl, and carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino,

they are attached form C1-C10 cycloalkyl; \mathbb{R}^1 and \mathbb{R}^2 taken together with the carbon to which

wherein R' and R' are as defined above; or heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹ consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, ${ t R}^3$ and ${ t R}^4$ are independently selected from the group

, or =CR¹¹R¹², R³ and R⁴ together form =0, =NOR¹¹, =S, =NNR¹¹R¹²

OR9, NR9R10, SR9, S(0)R9, SO2R9, SO3R9, CO2R9, CN, NH, and SH, or defined above, provided that both R^3 and R^4 cannot be OH, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, halogen, oxo, and CONR $^9\mathrm{R}^{10}$, wherein R^9 and R^{10} are as arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, the group consisting of H, alkyl, alkenyl, alkynyl, aryl, wherein \mathbb{R}^{11} and \mathbb{R}^{12} are independently selected from

atom to which they are attached form a cyclic ring; \mathbb{R}^{11} and \mathbb{R}^{12} together with the nitrogen or carbon

R⁵ is aryl substituted with one or more OR^{13b},

quaternary heterocyclylalkyl, quaternary heteroarylalkyl, of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, wherein ${ t R}^{{ t 13b}}$ is selected from the group consisting

 $m R^{13b}$ is substituted with one or more groups selected

from the group consisting of carboxyalkylheterocyclylthio, NR⁹R^{10a}, CONR⁹R^{10a},

SO2NR9R10a, p+R9R10aR11A-, and S+R9R10aA-,

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein R^{10a} is selected from the group consisting of carboxyalkyl, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, and heterocyclylalkyl; or

 R^6 is selected from the group consisting of H, alkyl, alkenyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, oxl³, NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, SO₂M¹³, NR¹³CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(0)OM, COR¹³, NR¹³C(0)R¹⁴, NR¹³COON, COCO)NR¹³R¹⁴, C(0)OM, COR¹³, NR¹³SOR¹⁴, NR¹³SO₄M¹⁴, S¹R¹³R¹⁴, P(0)R¹³R¹⁴, P(0)R¹³R¹⁴, pharein:

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be

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further substituted with one or more substituent groups selected from the group consisting of OR7, NR7R⁸, SR7, S(0)R⁷, SO₂R⁷, SO₂R⁷, CO₃R⁷, CN, OXO, CONR⁷R⁸, N⁴R⁷R⁸R⁹A-, alkyl, alkenyl, arkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(0)R⁷R⁸, P⁴R⁷R⁸R⁹A⁻, and P(0)(OR⁷)OR⁸, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N⁴R⁷R⁸A-, S, SO, SO₂, S⁴R⁷A-, PR⁷, P(O)R⁷, P⁴R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, heterocycle, heteroaryl, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by 0, NR', N'R'R'R'A-, S, SO, SO2, S'R'A-, PR', p'R'R'R'A-, P(O)R', phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R13, R14, and R15 are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclyjalkyl, quaternary heteroarylalkyl, guaternary heteroarylalkyl, guaternary heteroarylalkyl, guanidinyl, OR9, NR9R10, N+R9R11R12A-, SR9, S(O)R9,

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 SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M_f or

R" and R", together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 ${
m R}^{14}$ and ${
m R}^{15}$, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $^{\rm R}$ $^{\rm 7}$ and $^{\rm 8}$ are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, S(0)2R¹³, SO3R¹³, S⁺R¹³R¹⁴A-, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO2, CO2R¹³, CN, OM, SO2OM, SO2NR¹³R¹⁴, NR¹⁴C(0)R¹³, C(0)NR¹³R¹⁴, NR14C(0)R13, C(0)OM, COR¹³, OR¹⁸, S(0)NR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A-, amino acid, peptide, polypeptide, and

carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁴)OR¹⁷, P⁺R⁹R¹¹R¹²A⁻, S⁺R⁹R¹⁰A⁻, or C(O)OM, and

wherein R¹⁸ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N[†]R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, S0₂R⁹, S0₃R⁹, oxo, C0₂R⁹, CN, halogen, CONR⁹R¹⁰, S0₃R⁹, S0₂OM, S0₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and C(0)OM,

wherein in R^X , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A_-$, S, SO, SO₂, $S^+R^{13}A^-$, PR^{13} , $P(0)R^{13}$, $P^+R^{13}R^{14}A_-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR⁹, N⁺R⁹R¹⁰A⁻, s, s0, s0₂, s⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A⁻, or P(0)R⁹;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,

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- 56. A compound of claim 55 wherein:

 R¹ is phenyl substituted with OR¹¹⁹;

 R¹²⁹ is alkyl; and

 R¹¹⁹ is substituted with carboxyalkylheterocyclylthio or NR^{†R19}; and
 - R is hydrogen; and
- R10 is heteroarylalkyl.
- 57. A compound of claim 55 wherein n is 1 or 2.
- 58. A compound of claim 55 wherein R' and R' are independently selected from the group consisting of hydrogen and alkyl.
- 59. A compound of claim 55 wherein R' and R' are hydrogen.
- 60. A compound of claim 55 wherein R' and R' are independently selected from the group consisting of hydrogen and OR'.
- A compound of claim 55 wherein R' is hydrogen and R' is hydroxy.

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- 62. A compound of claim 55 wherein one or more R^a are independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$
- 63. A compound of claim 55 wherein one or more R are independently selected from methoxy and dimethylamino.
- 64. A compound of claim 55 wherein R' and R' are independently selected from the group consisting of hydrogen and alkyl.
- 65. A compound of claim 55 wherein R^1 and R^2 are independently selected from the group consisting alkyl.
- 66. A compound of claim 55 wherein R^1 and R^2 are the same alkyl.
- 67. A compound of claim 55 wherein R' and R' are each n-butyl.
- 68. A compound of claim 55 wherein
- n is 1 or 2;
- R and R are n-butyl;
- R' and R' are hydrogen; R' is hydroxy;
- R' and R' are hydrogen; and
- one or more $\ensuremath{\mathbb{R}}^x$ are independently selected from methoxy and dimethylamino.

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formula: 69. A compound of claim 55 having the structural

70. A compound of claim 55 having the structural formula:

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71. A compound of formula (I):

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wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

alkylthio, (polyalkyl) aryl, and cycloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, \mathbb{R}^1 and \mathbb{R}^2 are independently selected from the group

halogen, oxo, and CONR 9R 10, $s^* R^1 R^{10} A^*$. $p^+ R^9 R^{10} R^{11} A^*$, $s(0) R^9$, $so_2 R^9$, $so_3 R^9$, $co_2 R^9$, cw, alkylthio, (polyalkyl) aryl, and cycloalkyl optionally are the group consisting of OR9, NR9R10, N+R9R10RWA-, SR9, substituted with one or more substituents selected from alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, wherein alkyl, alkenyl, alkynyl, haloalkyl,

s, so, so₂, s⁺R⁹A, P⁺R⁹R¹⁰A, or phenylene, have one or more carbons replaced by O, NR⁹, N⁺R⁹R¹⁰A-, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy

cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, from the group consisting of H, alkyl, alkenyl, alkynyl wherein R^9 , R^{10} , and R^W are independently selected

carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

 ${
m R}^{1}$ and ${
m R}^{2}$ taken together with the carbon to which they are attached form C,-C,, cycloalkyl;

 R^3 and R^4 are independently selected from the group heterocycle, OR^3 , NR^3R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, wherein R' and R' are as defined above, or

R³ and R⁴ together form =0, =NOR¹¹, =S, =NNR¹¹R¹², -NR9, or -CR¹¹R¹²,

the group consisting of H, alkyl, alkenyl, alkynyl, aryl, wherein R¹¹ and R¹² are independently selected from defined above, provided that both \mathbb{R}^3 and \mathbb{R}^4 cannot be OH, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, halogen, oxo, and CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, CN, NH, and SH, or

 \mathbb{R}^{11} and \mathbb{R}^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

 ${\mathtt R}^{\mathsf S}$ is aryl substituted with one or more substituent groups independently selected from the group consisting OC(0) NR13R14, NR13SOR14, NR13SO₂R14, NR13SONR14R15, and of NR¹³C(0)R¹⁴, NR¹³C(0)NR¹⁴R¹³, NR¹³CO₃R¹⁴, OC(0)R¹³, NR11SO,NR14R15,

wherein:

R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl,

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quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary

one or more groups selected from the group consisting of SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, $\rm R^{13},\ R^{14},\ and\ R^{15}$ are optionally substituted with SO2NR9R10, PO(OR16)OR17, P*R9R10R11A-, S*R9R10A-, and hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, guanidinyl, OR^9 , NR^9R^{10} , $N^4R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quatermary heteroarylalkyl,

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R9 and M; or

R" and R", together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 ${\rm R}^{14}$ and ${\rm R}^{15}$, together with the nitrogen atom to which they are attached, form a cyclic ring; and

alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, S(O)R⁹, SO₂R⁹, and ${
m R}^6$ is selected from the group consisting of H,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

heterocycle, quaternary heterocycle, and quaternary heterocycle, guaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyatkyl, polyatkyl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, NR, NR¹³OR¹⁴, NR¹³R¹⁴, C(O)OM, COR¹³, NR¹³C(O)R¹⁴, SO₂OM, SO₂OM, SO₂OM, NR¹³R¹⁴, C(O)OM, SO₂OM, NR¹³R¹⁴, NR¹³CO,R¹⁴, OC(O)R¹³R¹⁴, NR¹³SOR¹⁴, NR¹³SOR¹⁴, NR¹³SOR¹⁴, NR¹³SOR¹⁴, NR¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻, wherein:

 ${\sf A}^-$ is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of oR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, CO₂R⁷, CN, oxo, CONR⁷R⁸, N⁺R⁷R⁸R⁹A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, p(O)R⁷R⁸, p⁺R⁷R⁸R⁹A-, and p(O)(OR⁷)OR⁸, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, R^7 , $N^+R^7R^8A$ -, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(0)R⁷, P⁺R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl,

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alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heterocyclylalkyl, heteroarylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl,

R¹³, R¹⁴, and R¹⁵ are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heterocryl, sulfoalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocrylalkyl, guanternary heterocrylalkyl, so, NR⁹R¹⁰, N⁴R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, so₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, pO (OR¹⁶) OR¹⁷, p⁴R⁹R¹⁰R¹¹A-, S⁴R⁹R¹⁰A-, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M, or

R¹¹ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl,

 $\rm R^7$ and $\rm R^8$ are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)2R¹³, SO₃R¹³, S⁺R¹³R¹⁴A⁻, NR¹³OR¹⁴, NR¹³CO₂R¹³, CO, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁶C(O)R¹³, C(O)RR¹³R¹⁴, NR¹⁶C(O)R¹³, C(O)RR¹³R¹⁸, NR¹⁸C(O)R¹³, OR¹⁸, S(O)_nNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻, p⁺R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹Rl⁰, N⁺R⁹Rl¹R¹Z^A, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹Rl⁰, SO₂OM, SO₂NR⁹Rl⁰, PO(OR¹¹)OR¹¹, P⁺R⁹Rl¹Rl²A⁻, S⁺R⁹Rl⁰A⁻, or C(0)OM, and

wherein \mathbb{R}^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group

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consisting of OR^9 , NR^9R^{10} , $N^4R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , Oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^{X} , one or more carbons are optionally replaced by 0, NR^{13} , $N^{+}R^{13}R^{14}A^{-}$, 8, 80, SO_{2} , $g^{+}R^{13}A^{-}$, PR^{13} , $P^{+}R^{13}R^{14}A^{-}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR⁹, N[†]R⁹R¹⁰A⁻, S, SO, SO₂, S[†]R⁹A⁻, PR⁹, P[†]R⁹R¹⁰A⁻, or P(0)R[†],

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, orl³, NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, SO₂R¹³, SO₂OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CM, OM, SO₂OM, SO₂NR¹³R¹⁴, C(0)NR¹³R¹⁴, C(0)OM, COR¹³, P(0)R¹³R¹⁴, p⁺R¹³R¹⁴R¹⁵A⁻, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

72. A compound of claim 71 wherein R⁵ is aryl substituted with a radical selected from the group consisting of NR¹³C(0)NR¹⁴R¹⁴ and NR¹³Co₂R¹⁴.

73. A compound of claim 71 wherein R' is phenyl substituted with a radical selected from the group

- 74. A compound of claim 71 wherein n is 1 or 2.
- hydrogen and alkyl. independently selected from the group consisting of 75. A compound of claim 71 wherein R' and R' are
- hydrogen. 76. A compound of claim 71 wherein R' and R' are
- hydrogen and OR'. independently selected from the group consisting of 77. A compound of claim 71 wherein R' and R' are
- R' is hydroxy. 78. A compound of claim 71 wherein R is hydrogen and
- and NR13R14. independently selected from the group consisting of OR" 79. A compound of claim 71 wherein one or more R* are
- independently selected from methoxy and dimethylamino. 80. A compound of claim 71 wherein one or more R* are
- hydrogen and alkyl. independently selected from the group consisting of 81. A compound of claim 71 wherein Ri and Ra are
- independently selected from the group consisting alkyl. 82. A compound of claim 71 wherein R1 and R2 are

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- same alkyl. 83. A compound of claim 71 wherein R and R are the
- n-butyl. 84. A compound of claim 71 wherein R1 and R2 are each
- 85. A compound of claim 71 wherein

n is 1 or 2;

R1 and R2 are n-butyl;

R' and R' are hydrogen;

R' is hydroxy;

R' and R' are hydrogen; and

and dimethylamino. one or more R' are independently selected from methoxy

86. Compound of claim 71 having the structural

87. A compound of claim 71 having the structural formula:

88. A compound of formula I:

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wherein:

q is 1 or 2,

n is 2;

R and R are each alkyl;

R' is hydroxy;

R' and R' are hydrogen,

R has the formula (II)

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Ξ

wherein t is an integer from 0 to 5;

one or more R' are OR13;

heteroaryl, quaternary heteroarylalkyl, and alkoxyalkyl, hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, alkylarylalkyl, cycloalkyl, heterocycle, ${\mathtt R}^{13}$ is selected from the group consisting of heteroaryl, quaternary heterocycle, quaternary

heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR, N'R'R"A', S, SO, SO, S'R'A', PR', P'R'R'A', P(O)R', phenylene, carbohydrate, said R¹³ alkyl, alkenyl, alkynyl, arylalkyl, amino acid, peptide, or polypeptide,

quaternary heterocycle, quaternary heteroaryl, OR', NR'R'', halogen, CONR'R10, SO,OM, SO,NR'R10, PO (OR14) OR17, P'R'R14R', groups selected from the group consisting of sulfoalkyl, \mathbb{R}^{13} is optionally substituted with one or more N'R'R1'R1'R1'R1'A', SR', S(0)R', SO,R', OXO, CO,R', CN, S'R'R'A', and C(0) OM,

wherein A' is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation,

R' and R' are independently selected from the group aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and consisting of H, alkyl, alkenyl, alkymyl, cycloalkyl, alkylammoniumalkyl;

R" and R" are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl,

substituents constituting R and M; to which they are attached form a cyclic ring; and provided that both R' and R' cannot be OH, NH, and SH; or oxo, and CONR'R', wherein R' and R' are as defined above, OR, NR, 10, SR, S(0)R, SO,R, SO,R, CO,R, CN, halogen, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, R^{16} and R^{17} are independently selected from the R' and R' are hydrogen; and R^{11} and R^{12} together with the nitrogen or carbon atom

group consisting of alkoxy, alkylamino and dialkylamino, one or more R* are independently selected from the

- prodrug thereof. a pharmaceutically acceptable salt, solvate, or
- each n-butyl. 89. A compound of claim 88 wherein R' and R' are
- OR^{13} , and R^{13} is as defined in claim 88. A compound of claim 89 wherein t is 1, R' is
- are independently selected from methoxy and dimethylamino. 91. A compound of claim 90 wherein one or more R*
- dimethylamino. 92. A compound of claim 90 wherein R* is
- t 18 1; A compound of claim 90 wherein:

R' is para-OR11; and

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t is 1; 94. A compound of claim 90 wherein:

RY is meta-OR13; and

R" is as defined in claim 88.

- configuration. 95. A compound of claim 90 having the 4R,5R
- compound of of any one of claims 1 to 95, and anti-hyperlipidemic condition effective amount of a a pharmaceutically acceptable carrier. 96. A pharmaceutical composition comprising an
- anti-atherosclerotic effective amount of a compound of any one of claims 1 to 95, and 97. A pharmaceutical composition comprising an
- a pharmaceutically acceptable carrier.
- of any one of claims 1 to 95, and anti-hypercholesterolemia effective amount of a compound 98. A pharmaceutical composition comprising an
- a pharmaceutically acceptable carrier.
- patient in need thereof a composition of claim 96 in unit hyperlipidemic condition comprising administering to a 99. A method for the prophylaxis or treatment of a
- patient in need thereof a composition of claim 97 unit atherosclerotic condition comprising administering to a dosage form. 100. A method for the prophylaxis or treatment of an
- hypercholesterolemia comprising administering to a 101. A method for the prophylaxis or treatment of

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patient in need thereof a composition of claim 98 in unit dosage form.

102. Use of a compound of any one of claims 1 to 95 in the preparation of a medicament for use in the prophylaxis or treatment of a hyperlipidemic condition.

103. Use of a compound of any one of claims 1 to 95 in the preparation of a medicament for use in the prophylaxis or treatment of an atherosclerotic condition.

104. Use of a compound of any one of claims 1 to 95 in the preparation of a medicament for use in the prophylaxis or treatment of hypercholesterolemia condition.

105. A process for the preparation of a compound having the formula:

106.

XĽ

comprising:

treating a thiophenol with an abstracting agent; coupling the thiophenyl and a cyclic sulfate to form an intermediate comprising a sulfate group; and removing the sulfate group of the intermediate to form the compound of formula XLI; wherein

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q is an integer from 1 to 4;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthlo, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR', NR'R'', N'R'R''R''S, SR', S'R'''R'', 'P'R''R''R'', S(O)R', SO,R', SO,R', CN, halogen, oxo, and CONR'R'',

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR',

N'R'R''A, S, SO, SO, S'R'A, P'R'R'A, or phenylene,
wherein R', R'', and R' are independently selected
from the group consisting of H, alkyl, alkenyl, alkynyl,
cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl,
arylalkyl, carboxyalkyl, carboxyheteroaryl,
carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino,
carboxyalkylaminoalkyl, heteroarylalkyl,
heterocyclylalkyl, and alkylammoniumalkyl; or

R, and R, taken together with the carbon to which they are attached form C,-C, cycloalkyl;

R' is hydroxy;

R* is hydrogen;

 $\rm R^5$ and $\rm R^6$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, $\rm QR^{30}$, $\rm SR^{9}$, $\rm S(O)R^{9}$, $\rm SO_2R^{9}$, and $\rm SO_3R^{9}$,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more

 $p^{+}R^{13}R^{14}R^{15}A^{-}$, $P(OR^{13})OR^{14}$, $S^{+}R^{13}R^{14}A^{-}$, and $N^{+}R^{9}R^{11}R^{12}A^{-}$ NR1350,R14, NR1350NR14R15, NR1350,NR14R15, P(0)R13R14 NR11C(0) NR11R15, NR11CO,R16, OC(0) R11, OC(0) NR11R16, NR11SOR16, SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $NR^{10}C(0)R^{14}$ ${\rm SO_{3}R^{13}}$, ${\rm NR^{13}OR^{14}}$, ${\rm NR^{13}NR^{14}R^{15}}$, ${\rm NO_{2}}$, ${\rm CO_{2}R^{13}}$, ${\rm CN}$, ${\rm OM}$, arylalkyl, quaternary heterocycle, quaternary heteroaryl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, consisting of alkyl, alkenyl, alkynyl, polyalkyl, halogen, ∞ 0, $0R^{13}$, $NR^{13}R^{14}$, SR^{13} , $S(0)R^{13}$, SO_2R^{13} substituent groups independently selected from the group

pharmaceutically acceptable cation, A is a pharmaceutically acceptable anion and M is

 $P(0)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(0)(0R^7)OR^8$, and arylalkyl, quaternary heterocycle, quaternary heteroaryl , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle S(0)R7, SO2R7, SO3R7, CO2R7, CN, OXO, CONR7R8, N+R7R8R9A. aryl, haloalkyl, cycloalkyl, and heterocycle can be selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , further substituted with one or more substituent groups said alkyl, alkenyl, alkynyl, polyalkyl, polyether,

alkylarylalkyl, alkylheteroarylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl selected from the group consisting of hydrogen, alkyl, NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R7, P+R7R8Acan optionally have one or more carbons replaced by 0, heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently polyether, aryl, haloalkyl, cycloalkyl, and heterocycle wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl,

acid, peptide, or polypeptide, and pR^9 , $p^+R^9R^{10}A$ -, $p(0)R^3$, phenylene, carbohydrate, amino carbons replaced by 0, NR', NTR'R'10A-, S, SO, SO2, STR'A heterocycle, and polyalkyl optionally have one or more

 $P^{+}R^{9}R^{10}R^{11}A-$, $S^{+}R^{9}R^{10}A-$, and C(0)OM, $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, O_{2} , O_{2} , O_{2} , O_{3} , O_{3} halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, guanidinyl, carboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰ heterocyclylalkyl, quaternary heteroarylalkyl heterocycle, quaternary heteroaryl, quaternary heterocycle, heteroaryl, sulfoalkyl, quaternary one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are optionally substituted with

the substituents constituting R9 and M; or wherein \mathbf{R}^{16} and \mathbf{R}^{17} are independently selected from

they are attached form a mono- or polycyclic heterocycle quaternary salts; or selected from the group consisting of oxo, carboxy and that is optionally substituted with one or more radicals R^{13} and R^{14} , together with the nitrogen atom to which

which they are attached, form a cyclic ring; and $m R^{14}$ and $m R^{15}$, together with the nitrogen atom to

alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, R30 is selected from the group consisting of alkyl,

carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R' and R' are hydrogen; and

NR''NR''R'' NO, CO,R'', CN, OM, SO,OM, SO,NR''R'', NR''C(O)R'', polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, one or more R* are independently selected from the NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)₃R¹³, SO₃R¹³, S'R¹³R¹⁴A', NR¹³OR¹⁴, C(0) NR¹³R¹⁴, NR¹⁴C(0) R¹³, C(0) OM, COR¹³, OR¹⁸, S(0) NR¹⁸, quaternary heterocycle, quaternary heteroaryl, oR¹³, NR¹³R¹⁸, NR¹⁸OR¹⁸, N'R¹R¹³R¹³R', P'R⁹R¹³R', amino acid, cycloalkyl, heterocycle, heteroaryl, polyether, group consisting of H, alkyl, alkenyl, alkynyl, peptide, polypeptide, and carbohydrate,

halogen, CONR*R19, SO,OM, SO,NR*R19, PO(OR16)OR17, P'R*R11R13A., wherein alkyl, alkenyl, alkymyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, heteroaryl can be further substituted with OR^{*} , $NR^{*}R^{*}$, polyether, quaternary heterocycle, and quaternary N'R'R11813A', SR', S(O)R', SO2R, SO3R', OXO, CO3R', CN, S'R'R'A', or C(0) OM, and

wherein R's is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, consisting of OR', NR'R'', N'R'R''R''A', SR', S(O)R', SO3R', SO,R', oxo, CO,R', CN, halogen, CONR'R1", SO,R', SO,OM, wherein acyl, arylalkoxycarbonyl, arylalkyl, one or more substituents selected from the group SO,NR'R1", PO (OR16) OR17, and C (O) OM,

wherein in R', one or more carbons are optionally wherein in said polyalkyl, phenylene, amino acid, replaced by O, NR¹³, N'R¹⁴8¹⁴, S, SO, SO₂, S'R¹³A⁻, PR¹³, polypeptide, carbohydrate, polyether, or polyalkyl, P(O)R13, P'R13R147, phenylene, amino acid, peptide,

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carbons are optionally replaced by O, NR, N'R'R'M', S, SO, peptide, polypeptide, and carbohydrate, one or more SO2, S'R'A', PR', P'R'R'A', or P(0)R';

P(O)R"B", P'R"R"R"A", P(OR")OR", S'R"R"A", and N'R'R"R"A". alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₃R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁴, NO₂ CO,R13, CN, OM, SO,OM, SO,NR13R14, C(O)NR13R14, C(O)OM, COR13 heteroaryl are optionally substituted with one or more cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹¹, groups selected from the group consisting of alkyl, wherein quaternary heterocycle and quaternary

106. The process of claim 105 wherein the cyclic sulfate has the formula:

¥

and the thiophenol has the formula:

wherein R', R', R' and q are as defined in claim

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105.

- group is removed by treating the intermediate with a hydrolyzing agent. 107. The process of claim 105 wherein the sulfate
- hydrolyzing agent is a mineral acid. 108. The process of claim 107 wherein the
- of hydrochloric acid and sulfuric acid. hydrolyzing agent is selected from the group consisting 109. The process of claim 107 wherein the
- 10. abstracting agent is a base having a pH of at least about 110. The process of claim 106 wherein the
- abstracting agent is an alkali metal hydride. 111. The process of claim 106 wherein the
- abstracting agent is sodium hydride. The process of claim 106 wherein the
- ethyl, n-butyl, iso-butyl and pentyl. independently selected from the group consisting of The process of claim 106 wherein R¹ and R² are

independently selected from alkyl.

113 The process of claim 106 wherein R' and R' are

The process of claim 106 wherein R and R are

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having the formula I: 116. A process for the preparation of a compound

$$\begin{array}{c|c}
(R_{1}^{N})_{q} & & & \\
\hline
(R_{2}^{N})_{q} & & & \\
\hline
(R_{3}^{N})_{q} & & & \\
\hline
(R_{3}^{$$

 Ξ

comprising:

an alcohol; reacting a cyclic sulfate with a thiophenol to form

oxidizing said alcohol to form a sulfone-aldehyde;

of formula I; cyclizing said sulfone-aldehyde to form the compound

wherein:

q is an integer from 1 to 4;

alkylthio, (polyalkyl) aryl, and cycloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, \mathbf{R}^1 and \mathbf{R}^2 are independently selected from the group

, P'R'R''R''A', S(0)R', SO3R', SO3R', CO3R', CN, halogen, oxo, the group consisting of OR', NR'R'', N'R'R''R'A', SR', S'R'R''A' alkylthio, (polyalkyl) aryl, and cycloalkyl optionally are alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, and CONR'R10, substituted with one or more substituents selected from wherein alkyl, alkenyl, alkynyl, haloalkyl,

alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR, wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy,

R' and R' taken together with the carbon to which are attached form C,-C, cycloalkyl; they

R' is hydroxy;

R' 1s hydrogen;

 R^{5} and R^{6} are independently selected from the group cycloalkyl, heterocycle, quaternary heterocycle, oR³⁰, consisting of H, alkyl, alkenyl, alkymyl, aryl, SR⁹, S(0)R⁹, SO2R⁹, and SO3R⁹,

arylalkyl, quaternary heterocycle, quaternary heteroaryl, ${
m SO_2OM},\ {
m SO_2NR^{13}R^{14}},\ {
m C(0)NR^{13}R^{14}},\ {
m C(0)OM},\ {
m COR^{13}},\ {
m NR^{13}C(0)R^{14}},$ P+R13R14R15A-, P(OR13)OR14, S+R13R14A-, and N+R9R11R12A-, substituent groups independently selected from the group wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, $NR^{12}C(0)NR^{14}R^{14}$, $NR^{13}CO_{4}R^{14}$, $OC(0)R^{13}$, $OC(0)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heterocycle, and quaternary halogen, ∞ o, $0 R^{13}$, $N R^{13} R^{14}$, $S R^{13}$, $S (0) R^{13}$, $S O_2 R^{13}$, ${
m SO_3R^{13}}$, ${
m NR^{13}OR^{14}}$, ${
m NR^{13}NR^{14}R^{15}}$, ${
m NO_2}$, ${
m CO_2R^{13}}$, ${
m CN}$, ${
m OM}$, consisting of alkyl, alkenyl, alkynyl, polyalkyl, heteroaryl can be substituted with one or more NR''SO,R'', NR''SONR''R'', NR''SO,MR''R''S, P(O)R¹³R¹⁴,

A ls a pharmaceutically acceptable anion and M is a

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pharmaceutically acceptable cation,

 $s(0)R^7$, so_2R^7 , so_3R^7 , co_2R^7 , cn, oxo, $conR^7R^8$, $n^4R^7R^8R^9A_4$. , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , aryl, haloalkyl, cycloalkyl, and heterocycle can be P(0)R7R8, p+R7R8R9A-, and P(0) (0R7)0R8, and

NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R7, P+R7R8A-, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, selected from the group consisting of hydrogen, alkyl, or phenylene, and ${\rm R}^{13}$, ${\rm R}^{14}$, and ${\rm R}^{15}$ are independently wherein said alkyl, alkenyl, alkymyl, polyalkyl, alkylarylalkyl, alkylheteroarylalkyl,

quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary

carbons replaced by O, NR', N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A., heterocycle, and polyalkyl optionally have one or more PR⁹, P⁺R⁹R¹⁰A-, P(O)R', phenylene, carbohydrate, amino wherein alkyl, alkenyl, alkynyl, arylalkyl, acid, peptide, or polypeptide, and

one or more groups selected from the group consisting of $R^{13},\ R^{14},\ and\ R^{15}$ are optionally substituted with hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary

 $P^{+}R^{9}R^{10}R^{11}A-$, $S^{+}R^{9}R^{10}A-$, and C(0)OM, $N^{+}R^{9}R^{12}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, OXO_{7} , OXO_{7} halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO (OR¹⁶) OR¹⁷, guanidinyl, carboxyalkylheterocyclylthio, OR9, NR9R10 heterocyclylalkyl, quaternary heteroarylalkyl,

the substituents constituting R9 and M; or wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected from

selected from the group consisting of oxo, carboxy and that is optionally substituted with one or more radicals they are attached form a mono- or polycyclic heterocycle quaternary salts; or R" and R", together with the nitrogen atom to which

which they are attached, form a cyclic ring; and \mathbb{R}^{14} and \mathbb{R}^{15} , together with the nitrogen atom to

heterocyclylalkyl, and alkylammoniumalkyl; and carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, haterocycle, R^{10} is selected from the group consisting of alkyl,

R' and R' are hydrogen; and

NR11R18, NR18OR14, N'R8R11R12A', P'R8R11R12A', amino acid, C(0)NR¹³R¹⁴, NR¹⁴C(0)R¹³, C(0)OM, COR¹³, OR¹⁸, S(0)_RNR¹⁸, NR11NR14R15, NO,, CO,R11, CN, OM, SO,OM, SO,NR11R14, NR14C(O)R11 NR11R14, SR11, S(0)R11, S(0),R11, SO,R11, STR11R14, NR11OR14, quaternary heterocycle, quaternary heteroaryl, OR13 cycloalkyl, heterocycle, heteroaryl, polyether, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, peptide, polypeptide, and carbohydrate, group consisting of H, alkyl, alkenyl, alkynyl, one or more R* are independently selected from the

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

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S'R'R10A', or C(O)OM, and N'R'R11R12A', SR', S(0)R', SO,R, SO,R', Oxo, CO,R', CN, halogen, CONR'R10, SO,OM, SO,NR'R10, PO(OR16)OR17, P'R'R11R13A, heteroaryl can be further substituted with OR', NR'R'', polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl,

heteroaryl, and alkyl, acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein R^{10} is selected from the group consisting of

SO₂NR⁹R¹⁰, PO (OR¹⁶) OR¹⁷, and C(O) OM, SO,R, oxo, CO,R, CN, halogen, CONR,R, SO,R, SO,OM, consisting of OR*, NR*R10, N'R*R11R11A', SR*, S(O)R*, SO,R*, one or more substituents selected from the group and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl,

polypeptide, carbohydrate, polyether, or polyalkyl, replaced by 0, NR13, N'R12R14A', S, SO, SO, S'R13A', PR13, P(0)R11, P'R11R14A', phenylene, amino acid, peptide, wherein in R*, one or more carbons are optionally

SO, S'R'A', PR', P'R'R'A', or P(O)R'; carbons are optionally replaced by O, NR, NRRNA, S, SO, peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

CO,R11, CN, OM, SO,OM, SO,NR11R14, C(O)NR11R14, C(O)OM, COR11 cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR11, NR11R14, SR11, S(O)R11, SO,R11, SO,R11, NR11OR14, NR11NR14R14, NO, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl P(0)R1R1, P'R11R1'R1'A, P(OR11)OR1, S'R11R1A, and N'R1R11R12 groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

sulfate has the formula: 117. The process of claim 116 wherein the cyclic

and the thiophenol has the formula: ¥

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wherein R', R', R' and q are as defined in claim 116.

- 118. The process of claim 117 wherein R' and R' are independently selected from alkyl.
- 119. The process of claim 117 wherein wherein R' and \mathbb{R}^2 are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.
- 120. The process of claim 117 wherein R' and R' are n-butyl.
- is oxidized with an oxidizing agent to form an aldehyde. 121. The process of claim 117 wherein the alcohol

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122. The process of claim 121 wherein the aldehyde is oxidized with an oxidizing agent to form a sulfonealdehyde.

123. The process of claim 117 wherein the sulfonealdehyde is cyclized with a cyclizing agent that is a base having a pH between about 8 to about 9. 124. The process of claim 117 wherein the sulfonealdehyde is cyclized with a cyclizing agent that is an alkali alkoxide base. 125. The process of claim 117 wherein the sulfonealdehyde is cyclized with potassium tert-butoxide.

metachloroperbenzoic acid to form a sulfone-aldehyde; and 126. The process of claim 117 wherein the alcohol is oxidized with pyridinium chlorochromate to form an the sulfone-aldehyde is cyclized with potassium tertaldehyde; the aldehyde is oxidized with butoxide.

127. A process for the preparation of a compound having the formula LI:

comprising:

treating a halobenzene with an abstracting agent, coupling the halobenzene and a cyclic sulfate to form an intermediate comprising a sulfate group; and

q is an integer from 1 to 4;

alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, R' and R' are independently selected from the group

wherein alkyl, alkenyl, alkynyl, haloalkyl,

alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, the group consisting of OR', NR'R'', N'R'R'A', SR', S'R'R''A substituted with one or more substituents selected from , P'R'R'A'A', S(0)R', SO,R', SO,R', CO,R', CN, halogen, oxo

alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR', wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy

carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino arylalkyl, carboxyalkyl, carboxyheteroaryl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, from the group consisting of H, alkyl, alkenyl, alkynyl, N'R'R''A', S, SO, SO, S'R'A', P'R'R''A', or phenylene wherein R', R'', and R' are independently selected

heterocyclylalkyl, and alkylammoniumalkyl; or carboxyalkylaminoalkyl, heteroarylalkyl, R' and R' taken together with the carbon to which

they are attached form C3-C30 cycloalkyl; R' is hydroxy;

R' is hydrogen;

consisting of H, alkyl, alkenyl, alkynyl, aryl, \mathtt{R}^S and \mathtt{R}^G are independently selected from the group

 SR^9 , $S(0)R^9$, SO_2R^9 , and SO_3R^9 , cycloalkyl, heterocycle, quaternary heterocycle, oR30

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

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p+R¹³R¹⁴R¹⁵A-, P(OR¹³)OR¹⁴, S+R¹³R¹⁴A-, and N+R⁹R¹¹R¹²A-, ${\rm SO_3R^{13}}$, ${\rm NR^{13}OR^{14}}$, ${\rm NR^{13}NR^{14}R^{15}}$, ${\rm NO_2}$, ${\rm CO_2R^{13}}$, ${\rm CN}$, ${\rm OM}$, NR"30,R", NR"SONR"R", NR"SO,NR"R", P(O)R13R14 NR12C(0)NR14R15, NR12CO,R14, OC(0)R11, OC(0)NR12R14, NR12SOR14, SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $NR^{10}C(0)R^{14}$ polyether, aryl, haloalkyl, cycloalkyl, heterocycle, halogen, cxc, cR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} arylalkyl, quaternary heterocycle, quaternary heteroaryl, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heteroaryl can be substituted with one or more heterocycle, quaternary heterocycle, and quaternary wherein:

pharmaceutically acceptable cation, A is a pharmaceutically acceptable anion and M is

 $P(0)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(0)(0R^7)0R^8$, and arylalkyl, quaternary heterocycle, quaternary heteroaryl , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, s(0)R', s02R', s03R', c02R', cN, oxo, conr'R', N'R'R'R'Aaryl, haloalkyl, cycloalkyl, and heterocycle can be selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , further substituted with one or more substituent groups said alkyl, alkenyl, alkynyl, polyalkyl, polyether

alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl selected from the group consisting of hydrogen, alkyl, or phenylene, and R^{13} , R^{14} , and R^{15} are independently NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R7, P+R7R8Acan optionally have one or more carbons replaced by O, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle alkylarylalkyl, alkylheteroarylalkyl, wherein said alkyl, alkenyl, alkynyl, polyalkyl,

alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by 0, NR', $N^+R^2R^{10}A^-$, S, S0, S02, S^+R^3A , PR^9 , $P^+R^9R^{10}A^-$, $P(0)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R¹³, R¹⁴, and R¹⁵ are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, suboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, p⁺R⁹R¹⁰R¹¹A-, S⁺R⁹R¹⁰A-, and C(O)OM,

wherein $\rm R^{16}$ and $\rm R^{17}$ are independently selected from the substituents constituting $\rm R^9$ and M; or

R¹³ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and R^{10} is selected from the group consisting of alkyl, alkynyl, cycloshkyl, aryl, acyl, heterocycle,

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ammoniumalkyl, alkylanmoniumalkyl, arylalkyl,
carboxyalkyl, carboxyheteroaryl, carboxyheterocycle,
carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl,
heterocyclylalkyl, and alkylammoniumalkyl; and

R' and R' are hydrogen; and

one or more R^{*} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, fereroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, oR¹³, NR¹³K¹⁴, SR¹³, S(0)R¹³, S(0)R¹³, SO₁R¹³, SO₂R¹³, SO₃R¹³, SO₃R¹³, NR¹³K¹⁴, NR¹³C(0)R¹³, C(0)NR¹³K¹⁴, NR¹³C(0)R¹³, C(0)OM, COR¹³, OR¹³, SO₃NR¹⁴, NR¹³C(0)R¹³, C(0)M, COR¹³, OR¹³, SO₃NR¹⁴, NR¹³C(0)R¹³, C(0)M, COR¹³, OR¹³, SO₃NR¹⁴, NR¹³C¹³, NR

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR*, NR*N*, NR*N*R*, S(O)R*, SO,R, SO,R*, oxo, CO,R*, CN, halogen, CONR*R*, SO,OM, SO,NR*N*, PO(OR*)OR*, PY*R*N*A; S'R*N*A, or C(O)OM, and

wherein R¹⁸ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR', NR'R'R'R'A', SR', S(O)R', SO,R', SO,R', CN, halogen, CONR'R'', SO,R', SO,R', SO,R', and C(O)OM,

wherein in R, one or more carbons are optionally replaced by O, NR¹³, N'R¹³R¹⁴A', S, SO, SO, S'R¹³A', PR¹³, P(O)R¹³, P'R¹³R¹⁴A', phenylene, amino acid, peptide,

SO, S'R'A', PR', P'R'R'A', or P(0)R'; carbons are optionally replaced by O, NR, NTRRA, S, SO, peptide, polypeptide, and carbohydrate, one or more polypeptide, carbohydrate, polyether, or polyalkyl, wherein in said polyalkyl, phenylene, amino acid,

P(0)R12R1, P'R12R14R14R14, P(OR12)OR14, S'R12R14A, and N'R12R14A CO,R13, CN, OM, SO,OM, SO,NR13R14, C(O)NR13R14, C(O)OM, COR13, NR11R14, SR13, S(0)R13, SO,R13, SO,R13, NR11OR14, NR13NR14R15, NO, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR11 alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

para or ortho position. R° is an electron-withdrawing group located at the

sulfate has the formula: 128. The process of claim 127 wherein the cyclic

ž

and the halobenzene has the formula:

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as defined in claim 127. wherein Rh is halogen, and R1, R2, R4, R4, R4 and q are

- group is removed by treating the intermediate with a hydrolyzing agent. 129. The process of claim 128 wherein the sulfate
- hydrolyzing agent is a mineral acid. 130. The process of claim 129 wherein the
- of hydrochloric acid and sulfuric acid. hydrolyzing agent is selected from the group consisting 131. The process of claim 129 wherein the
- abstracting agent is a dialkali metal sulfide. 132. The process of claim 128 wherein the
- abstracting agent is dilithium sulfide. The process of claim 128 wherein the
- R' are independently selected from alkyl. 134. The process of claim 128 wherein wherein R and
- ethyl, n-butyl, iso-butyl and pentyl. independently selected from the group consisting of 135. The process of claim 128 wherein R' and R'
- n-butyl. 136. The process of claim 128 wherein R' and R' are
- 137. The process of claim 128 wherein Rh is chloro.
- 138. The process of claim 128 wherein R is p-nitro.
- A process for the preparation of a compound

 $\widehat{\Xi}$

comprising:

reacting a cyclic sulfate with a halobenzene to form an alcohol;

oxidizing said alcohol to form a sulfone-aldehyde, and cyclizing said sulfone-aldehyde to form the compound of formula I;

wherein

q is an integer from 1 to 4;

n 18 2;

R' and R' are independently selected from the group alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylthio, (polyalkyl) aryl, and cycloalkyl,

alkylthio, (polyalkyl) aryl, and cycloalkyl optionally are the group consisting of OR', NR'R', N'R'R'R'R', SR', S'R'R'A' alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, , P'R'R'R'B'1'A', 8(0)R', SO;R', SO;R', CO;R', CN, halogen, oxo, substituted with one or more substituents selected from wherein alkyl, alkenyl, alkynyl, haloalkyl, and CONR'R1º,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR',

N'R'R'8'A', S, SO, SO, S'R'A', P'R'R'A', or phenylene, wherein R', R'', and R' are independently selected

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from the group consisting of H, alkyl, alkenyl, alkynyl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, heterocyclylalkyl, and alkylammoniumalkyl, or arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyalkylaminoalkyl, heteroarylalkyl,

R' and R' taken together with the carbon to which they are attached form C,-C, cycloalkyl,

R' is hydroxy;

R' is hydrogen;

 ${
m R}^5$ and ${
m R}^6$ are independently selected from the group cycloalkyl, heterocycle, quaternary heterocycle, oR³⁰, consisting of H, alkyl, alkenyl, alkynyl, aryl, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹,

arylalkyl, quaternary heterocycle, quaternary heteroaryl, ${
m SO_2OM},\ {
m SO_2NR}^{13}{
m R}^{14},\ {
m C(0)}\,{
m NR}^{13}{
m R}^{14},\ {
m C(0)}\,{
m OM},\ {
m COR}^{13},\ {
m NR}^{13}{
m C(0)}\,{
m R}^{14},$ P*R13R14R15A, P(OR13)OR14, S*R13R14A, and N*R9R11R12A-, substituent groups independently selected from the group wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, NR¹²C(O)NR¹⁴R¹⁵, NR¹³CO₂R¹⁴, OC(O)R¹³, OC(O)NR¹³R¹⁴, NR¹³GOR¹⁴, heterocycle, quaternary heterocycle, and quaternary polyether, aryl, haloalkyl, cycloalkyl, heterocycle, SO3R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³ consisting of alkyl, alkenyl, alkynyl, polyalkyl, heteroaryl can be substituted with one or more NR13SO,R14, NR11SONR14R13, NR12SO,NR14R15, P(O)R13R14,

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether,

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R7, P+R7R8A-, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle alkylarylalkyl, alkylheteroarylalkyl, selected from the group consisting of hydrogen, alkyl, or phenylene, and R^{13} , R^{14} , and R^{15} are independently can optionally have one or more carbons replaced by O, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle wherein said alkyl, alkenyl, alkynyl, polyalkyl,

acid, peptide, or polypeptide, and pR^9 , $p^+R^9R^{10}A^-$, $P(0)R^*$, phenylene, carbohydrate, amino carbons replaced by 0, NR, N † R 9 R 10 A-, s, s0, s0 $_{2}$, s † R 9 A heterocycle, and polyalkyl optionally have one or more wherein alkyl, alkenyl, alkynyl, arylalkyl,

guanidinyl, carboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰, heterocyclylalkyl, quaternary heteroarylalkyl, heterocycle, quaternary heteroaryl, quaternary heterocycle, heteroaryl, sulfoalkyl, quaternary hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, one or more groups selected from the group consisting of $m R^{13},~R^{14}$, and $m R^{15}$ are optionally substituted with

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 $P^{+}R^{9}R^{10}R^{11}A-$, $S^{+}R^{9}R^{10}A-$, and C(O)OM, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷ $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, OXO_{4} , $CO_{2}R^{9}$, CN,

the substituents constituting R9 and M; or R13 and R34, together with the nitrogen atom to which wherein R¹⁶ and R¹⁷ are independently selected from

quaternary salts; or selected from the group consisting of oxo, carboxy and that is optionally substituted with one or more radicals they are attached form a mono- or polycyclic heterocycle

which they are attached, form a cyclic ring; and ${{ t R}^{14}}$ and ${{ t R}^{15}}$, together with the nitrogen atom to

heterocyclylalkyl, and alkylammoniumalkyl; and carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, R30 is selected from the group consisting of alkyl

R' and R' are hydrogen; and

C(0)NR13R14, NR14C(0)R13, C(0)OM, COR13, OR16, S(0) NR16 NR11NR11'R11, NO, CO2R11, CN, OM, SO2OM, SO2NR11'R11, NR11C(O)R11, NR11R1, SR1, S(0)R1, S(0)R1, S0'R1, S1R11R1, NR110R1 quaternary heterocycle, quaternary heteroaryl, OR13 group consisting of H, alkyl, alkenyl, alkynyl, peptide, polypeptide, and carbohydrate, NR12R1, NR16OR1, N'R'R12R12A', P'R'R11R12A', amino acid, cycloalkyl, heterocycle, heteroaryl, polyether, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl one or more R* are independently selected from the

polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, heteroaryl can be further substituted with OR, NR'R10 polyether, quaternary heterocycle, and quaternary wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl

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Nrkhiria', sr', s(o)r', so,r, so,r', oxo, co,r', cn, halogen, conr'r', so,om, so,nr'r'', po(or'')or'', p'r'r''r', S'r'r'a', or c(o)om, and wherein R¹⁸ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR, NR*R*, NR*R*, SR*, S(O)R*, SO,R*, SO,R*, CN, halogen, CONR*R*, SO,R*, SO,OM, SO,NR*R*, PO(OR**)OR!*, and C(O)OM,

wherein in R*, one or more carbons are optionally replaced by 0, NR¹, N'R¹, S, S0, S0, S'R¹, PR¹, PR¹, P(0)R¹, P'R¹, P'R¹, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, wherein in said nolyalkyl, phenylene, amino acid

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR*, N'R*R*A, S, SO, SO, S'R*A, PR*, P'R*R*A, or P(0)R*;

R° is an electron-withdrawing group located at the para or ortho position.

140. The process of claim 139 wherein the cyclic sulfate has the formula:

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;

and the halobenzene has the formula:

wherein $R^1,\ R^2,\ R^2$ and R^n are as defined in claim 139, and R^n is halogen.

141. The process of claim 140 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.

142. The process of claim 141 wherein the hydrolyzing agent is a mineral acid.

143. The process of claim 140 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.

144. The process of claim 140 wherein the abstracting agent is a dialkali metal sulfide.

145. The process of claim 140 wherein the abstracting agent is dilithium sulfide.

- independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl. 147. The process of claim 140 wherein R' and R' are
- n-butyl. 148. The process of claim 140 wherein R¹ and R² are
- 149. The process of claim 140 wherein Rh is chloro.
- 150. The process of claim 140 wherein R° is p-nitro
- is oxidized with an oxidizing agent to form a sulfone. 151. The process of claim 140 wherein the alcohol
- aldehyde. is oxidized with an oxidizing agent to form a sulfone-152. The process of claim 140 wherein the sulfone
- base having a pH between about 8 to about 9. aldehyde is cyclized with a cyclizing agent that is a 153. The process of claim 140 wherein the sulfone-
- alkali alkoxide base. aldehyde is cyclized with a cyclizing agent that is an 154. The process of claim 140 wherein the sulfone-
- aldehyde is cyclized with potassium tert-butoxide. 155. The process of claim 140 wherein the sulfone-
- is oxidized with metachloroperbenzoic acid to form a 156. The process of claim 140 wherein the alcohol

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butoxide. sulfone-aldehyde is cyclized with potassium tertchlorochromate to form a sulfone-aldehyde; and the sulfone; the aldehyde is oxidized with pyridinium

INTERNATIONAL SEARCH REPORT

		PCT/US	PCT/US 99/12828
A. CLASSE IPC 7	1.0.45smcAndwgv 8up.ecf MATTER 1PC 7 C070337/08 C070487/08 C070409/12 C07F9/6553 C07C323/18 A61X31/38	. C070409/10	C07K5/06
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	page 75 -page 183; claims		?
⋖	WO 96 08484 A (MONSANTO) 21 March 1996 (1996-03-21) the whole document		1-3,21, 38,95-97
×.	WO 98 40375 A (G.O.SEARE) 17 September 1998 (1998-09-17) page 66 -page 127; claims; example	le 1400	1-3,71, 95-127
ш	WO 99 32478 A (G.D. SEARLE) 1 July 1999 (1999-07-01) the whole document		1,105-149
	Further documents are fated in the continuation of box C.	X Petert lamby members are tated in errex.	lated in errory.
'A' docum	Special categories of cled documents; A. document defiving the parent state of the an which is not considered to be of particular reference.	This ister document published after the International litting data or priority data and not in contid with the application but client to understand the principle or theory underlying the investrian	International titing data with the application but or theory underlying the
in the state of th	softer document but puddined on or after the international filling data. They data and other sources or priority cashital or within any drow doubts on priority cashital or within a died to establish the publication data of smother within a died to establish the publication data of smother.	"X" document of particular relevance; the claimed invention cannot be considered from or cannot be considered to trovide an inventive stop when the occurrent is laten alone "Y" document of particular relevance; the claimed invention	the claimed invention tarmot be conclosed to the document in taken alone the claimed invention
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Name and matthy address of the ISA European Petrist Office, P. 8. 5518 Peterstann 2 Nr. – 2500 Nr. Playedt 14. (-511–71) 340–501 T. 51 651 spo nr. Fez: (-511–71) 340–5016

Francois, J

08/11/1999 Authorized officer

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Data of the actual completion of the international search 28 October 1999

INTERNATIONAL SEARCH REPORT

metional application No. PCT/US 99/12828

 Box I Observations where certain cisi	Observations where certain claims were found unsearchable (Continuation of item 1 of first aheat)	\top
 This international Search Report has not been e	This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the Kolowing reasons:	
 f. X Clama Nox: 99 to 101 Remark: Although claims 99 to 101 Remark: Although claims 99 to 101 are directed to a diagnos body, the search has been effects of the compound/c	99 to 101 Nemark: Although claims 99 to 101 Remark: Although claims 99 to 101 Remark: Although claims 99 to 101 are directed to a diagnostic method practised of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.	
Carra Nos.: because they reitie to parts of the inte an extent that no meaningful internation	Claims Nos.: because they relate to parts of the international Application that do not compty with the prescribed requirements to such an actent that no meantighal international Search can be carried out, specifically:	
 3. Claims Nos.: because Day are dependent claims or	Claims Nos.: berause they are dependent claims and are not chafted in accordance with the second and third sentences of Rule 6.4(s).	
Box II Observations where unity of Inv	Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)	
This international Searchting Authority found mi	This international Searching Authority found multiple inventions in this unternational application, as follows:	
As all required additional search less to searcheble claims.	As all required additional search less were threnty paid by the applicant, this international Search Report covers at searchable chains.	
As all eserchable claims could be sear of any additional ite.	As at secritable datms could be searched without after justifying an additional fee, this Authority did not invite payment of any additional file.	
3. As only some of the required addition overs only those claims for which fee	As only some of the required additional asarch less were timely paid by the applicant, this international Search Report covers only those claims for which less were paid, specifically claims Note.	
4. We required additional search fees we restricted to the invention first membor	No required additional search frees were thinly paid by the applicant, Cornsequently, this International Search Report is restricted to the invention litest mentioned in the claims: it is covered by claims Nos.:	
Remark on Protest	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search less.	

Form PCTASAZ10 (continuation of first sheet (1)) (July 1998)

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unformation on patent family members

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C07D 337/08, 487/08, 409/12, 409/10, C07K 5/06, C07F 9/6553, C07C 323/18, A61K 31/38	<u>^1</u>	13 Janu
(21) International Application Number: PCT/US	PCT/US99/12828	(74) Common Representative: G.D. SEARLE & CO.; Williams, Roger, A., Concorate Patent Department, P.O. Box 5110.
(22) International Filing Date: 29 June 1999 (29.06.99)	29.06.99)	Chicago, IL 60680 (US).
(30) Priority Data: 09/109.551 2 July 1998 (02.07.98)	US.	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, FRE, HU, ID, IL, IS, JP, KE, KG, KP, KR,
(71) Applicant (for all derignated States except US); G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).	SEARLE 9.0. Box	MY, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TI, TM, TR, TT, UA, UG, US, UZ, VN, VU, ZA, ZW, ARTO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW). Euralian patent (AM, AZ, BY, KG, KZ, MD, RU, TL, ZW).
(72) Inventors; and (75) Inventors Applicants (for US only): LEE, Len, F. [USUS]; (75) Inventors Applicants (for US only): LEE, Len, F. [USUS]; 2,495 Annapolit Way, St. Charles, Mt. 63303 (US). BANERJEE, Shyamai, C. [USUS]; 13567 Country Ridge BANERJEE, Shyamai, C. [USUS]; 13567 Country Ridge Drive, Chasterfield, MO 33017 (US). HUANG, HONG-Chill Late; 14,681 [Un-then Use, Country Aug 2407 (US).	TUS/US); 3 (US). 7 Ridge mg—Chih	TM), European patent (AT, BE, CH, CY, DE, DK, ES, Ft, Ft, GB, GR, IE, IT, LU, MC, NL, FT, SE), OAPI patent GR; BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
LI, Jinglin, J. (USVUS), 76 Szandord Road East, Penningrod, NI 08534 (US), MILLER, Raymond, E. (USVUS), 1994 Old Lincoln Trail, Fairview Heighta, II. 62208 (US), REITZ, David, B. (USVUS); 1481 4 Picasann Ridge, Chesterfield, MO 63017 (US), TREMONT, Samuel, J. [USVUS]; 729 Berquist Drive, St. Louis, MO 63011 (US).	nington, 9904 Old REITZ, held, MO Berquist	Published With international search report. Before the expiration of the time limit for amending the Claims and to be republished in the event of the receipt of amendments.

Novel benzothlepines, derivatives, and analogs thereof, methods of preparing such compounds; pharmaceulcal compositions containing such compounds; and methods of using these compounds and compositions in the preparation of a medicament, particularly medicaments for use in the prophylaxis and treatment of hypertipidemic conditions such as those associated with atherosclerosis or hypertholesterotemia, in mammals.

(54) THE: BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

(57) Abstract

*(Referred to in PCT Cazette No. 29/2000, Section II)

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OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

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pharmaceutical compositions containing them, and their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as is benzothiepines, derivatives and analogs thereof, The present invention relates to novel associated with atherosclerosis or hypercholesterolemía, in mammals.

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Description of Related Art

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It is well-settled that hyperlipidemic conditions state of atherosclerosis. Stedronsky, in "Interaction are major risk factors for coronary heart disease and such reduction leads to an improvement in the disease of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et particularly atherosclerosis. Interfering with the Epidemiological data has accumulated which indicates cholesterol and low-density lipoprotein cholesterol Biophysica Acta, 1210 (1994) 255-287 discusses the circulation of bile acids within the lumen of the intestinal tract is found to reduce the levels of associated with elevated concentrations of total biochemistry, physiology and known active agents serum cholesterol in a causal relationship. surrounding bile acids and cholesterol.

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stional applications under the PCT.

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Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic

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circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport",

Gastroenterology, 1982:83:804-11.

levels. of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol the liver using cholesterol as well as an upregulation results in an increase in liver bile acid synthesis by treatment", Atherosclerosis, 89(1991) 183-190). This excretion in the hamster with cholestyramine Suckling el al, "Cholesterol Lowering and bile acid CoA reductase activity and low density lipoprotein Lipid Research, Volume 31, 1990, 2219-2226 and receptor expression in gallstone patients", Journal of humans: stimulatory effects of cholestyramine on HMGin "Regulation of hepatic cholesterol metabolism in normal enterchapatic circulation (Reihnér, E. et al, the intestinal tract, thereby interfering with their In fact, cholestyramine binds the bile acids in

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In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 25, pp. 18035-18046, 1993).

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In a series of patent applications, e.g. Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including

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bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents.

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In vitro bile acid transport inhibition is disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds"

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Selected benzothiepines are disclosed in world patent application number W093/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

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The above references show continuing efforts to find safe, effective agents for the prophylaxis and treatment of hyperlipidemic diseases and their usefulness as hypocholesterolemic agents.

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Additionally selected benzothiepines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

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The present invention furthers such efforts by providing novel benzothiepines, pharmaceutical compositions, and methods of use therefor.

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SUMMARY OF THE INVENTION

present invention provides compounds of formula (I): Accordingly, among its various apects, the

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wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

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haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, ${\rm R}^1$ and ${\rm R}^2$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, dialkylamino, alkylthio, (polyalkyl) aryl, and

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cycloalkyl optionally are substituted with one or more OR9, NR9R10, N'R9R10R"A", SR9, S'R'R"A". P'R9R10R11A" substituents selected from the group consisting of $s(0)R^9$, so_2R^9 , so_3R^9 , co_2R^9 , cN, halogen, oxo, and wherein alkyl, alkenyl, alkynyl, haloalkyl, dialkylamino, alkylthio, (polyalkyl) aryl,"and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, cycloalkyl,

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alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR9, N+R9R10A-, S, SO, SO2, S+R9A', P+R9R10A', or wherein alkyl, alkenyl, alkynyl, alkylaryl,

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phenylene,

alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, selected from the group consisting of H, alkyl, wherein R⁹, R¹⁰, and R^W are independently heterocyclylalkyl, and alkylammoniumalkyl; or carboxyalkylaminoalkyl, heteroarylalkyl, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino,

 R^1 and R^2 taken together with the carbon to which they are attached form C,-C,, cycloalkyl;

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acyloxy, aryl, heterocycle, oR^9 , NR^9R^{10} , SR^9 , $S(0)R^9$, R³ and R⁴ are independently selected from the SO2R9, and SO3R9, wherein R° and R10 are as defined group consisting of H, alkyl, alkenyl, alkynyl, above; or

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R³ and R⁴ together form =0, =NOR¹¹, =S, "NNR¹¹R¹², "NR⁹, or "CR¹¹R¹²,

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wherein ${ t R}^9$ and ${ t R}^{10}$ are as defined above, provided that alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl ${
m SO_2R}^9$, ${
m SO_3R}^9$, ${
m CN}$, ${
m CN}$, halogen, ${
m oxo}$, and ${
m CONR}^9{
m R}^10$, wherein R^{11} and R^{12} are independently selected cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, from the group consisting of H, alkyl, alkenyl, neterocycle, carboxyalkyl, carboalkoxyalkyl,

 R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring; both R3 and R4 cannot be OH, NH,, and SH, or

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group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR 9 ${\rm R}^5$ and ${\rm R}^6$ are independently selected from the

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SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heterocycle, and quaternary heterocycle, and squaternary heterocycle, and the group consisting of alkyl, alkenyl, alkenyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, SO₂R¹³, SO₂R¹³, SO₃R¹³, NR¹³O₂R¹⁴, NR¹³SO₂R¹⁴, OC(O)MR¹³R¹⁴, C(O)MR¹³R¹⁴, C(O)MR¹³R¹⁴, C(O)MR¹³R¹⁴, OC(O)R¹³, OC(O)MR¹³R¹⁴, NR¹³SO₂R¹⁴, NR¹³R¹⁴, NR¹³SO₂R¹⁴, NR¹³R¹⁴, NR¹³SO₂R¹⁴, NR¹³R¹⁴, NR¹³SO₂R¹⁴, NR¹³R¹⁴, NR¹³

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wherein:

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A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, said alkyl, alkenyl, alkynyl, polyalkyl,

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polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, SO₃R⁷, CO₂R⁷, CO₂R⁷, CO₂R⁷, CO₂R⁷, CO₃R⁷, SO₃R⁷, SO₃R⁷, Alkyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl,

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 $p(0)R^7R^8$, $p^+R^7R^8R^9A^-$, and p(0) ($0R^7$) $0R^8$, and wherein said alkyl, alkenyl, alkynyl, polyalkyl polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons

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10 20 15 30 25 polyether, aryl, arylalkyl, alkylarylalkyl, of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, are independently selected from the group consisting P(O)R7, PtR7R8A-, or phenylene, and R13, R14, and R15 carbohydrate, amino acid, peptide, or polypeptide, and $s^+R^9A^-$, pR^9 , $p^+R^9R^{10}A^-$, $P(0)R^9$, phenylene, carbons replaced by 0, NR 9 , N 4 R 9 R 10 A-, S, S0, S02. carboxyalkylaminocarbonylalkyl, quaternary heteroarylalkyl, alkoxyalkyl, heteroarylalkyl, quaternary heterocyclylalkyl heterocycle, quaternary heteroaryl, heterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary alkylheteroarylalkyl, alkylheterocyclylalkyl, replaced by 0, NR^7 , $N^{\dagger}R^7R^8A^-$, s, so, so2, s $^{\dagger}R^7A^-$, PR^7 $_{
m N^+R^9R^{11}R^{12}A^-}$, $_{
m SR^9}$, $_{
m S(O)R^9}$, $_{
m SO_2R^9}$, $_{
m SO_3R^9}$, $_{
m oxo}$, $_{
m CO_2R^9}$ quaternary heterocycle, quaternary heteroaryl, of hydroxy, amino, sulfo, carboxy, alkyl, one or more groups selected from the group consisting heterocycle, and polyalkyl optionally have one or more $_{p}^{+}_{R}^{9}_{R}^{10}_{R}^{11}_{A-}$, $_{S}^{+}_{R}^{9}_{R}^{10}_{A-}$, and C(0)OM, carboxyalkylheterocyclylthio, OR9, NR9R10, heteroarylalkyl, guanidinyl, quaternary heterocyclylalkyl, quaternary carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, alkylammoniumalkyl, and CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷ which they are attached form a mono- or polycyclic from the substituents constituting R^9 and M_i or $m R^{13}$, $m R^{14}$, and $m R^{15}$ are optionally substituted with wherein alkyl, alkenyl, alkynyl, arylalkyl, ${\mathbb R}^{13}$ and ${\mathbb R}^{14}$, together with the nitrogen atom to wherein $\mathbf{R}^{\mathbf{16}}$ and $\mathbf{R}^{\mathbf{17}}$ are independently selected

heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R¹⁴ and R¹⁵, together with the nitrogen atom to which they are attached, form a cyclic ring; and

 \mathbb{R}^7 and \mathbb{R}^8 are independently selected from the group consisting of hydrogen and alkyl; and

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one or more \mathbb{R}^{X} are independently selected from ${
m p^+R^9R^{11}R^{12}A^-}$, amino acid, peptide, polypeptide, and the group consisting of H, alkyl, alkenyl, alkynyl, heteroaryl, $o \mathrm{R}^{13}$, $\mathrm{NR}^{13} \mathrm{R}^{14}$, SR^{13} , $\mathrm{S}(\mathrm{O}) \mathrm{R}^{13}$, $\mathrm{S}(\mathrm{O}) \mathrm{2R}^{13}$, haloalkyl, cycloalkyl, heterocycle, heteroaryl, SO3R¹³, S⁺R¹³R¹⁴A-, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, polyether, quaternary heterocycle, quaternary $C(0) NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, C(0)OM, COR^{13} , OR^{18} , \cos^{13} , CN, OM, \cos_2 OM, \cos_2 NR 13 R 14 , NR 14 C(O)R 13 , polyalkyl, acyloxy, aryl, arylalkyl, halogen, S(O)_nNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻, carbohydrate,

PO(OR16)OR17, P+R9R11R12A-, S+R9R10A-, or C(0)OM, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, haloalkyl, polyether, quaternary heterocycle, and wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl,

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wherein $R^{f 18}$ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle,

heterocycle, and quaternary heteroaryl optionally are wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary

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from the group consisting of OR 9 , $m NR^9R^{10}$, $m N^+R^9R^{11}R^{12}A^-$, sR^9 , $s(0)R^9$, so_2R^9 , so_3R^9 , oxo, co_2R^9 , CN, halogen, $conr^{9}r^{10}$, so_3r^{9} , so_2om , $so_2nr^{9}r^{10}$, $ro(or^{16})or^{17}$, and substituted with one or more substituents selected C(0) OM, wherein in R^{X} , one or more carbons are optionally replaced by O, NR¹³, N⁺R¹³R¹⁴A-, S, SO, SO₂, S⁺R¹³A⁻, peptide, polypeptide, carbohydrate, polyether, or pR^{13} , $P(0)R^{13}$, $p^+R^{13}R^{14}A^-$, phenylene, amino acid,

wherein in said polyalkyl, phenylene, amino acid, carbons are optionally replaced by 0, NR 9 , N $^+$ R 9 R 1 O $_A$ peptide, polypeptide, and carbohydrate, one or more s, so, so2, s+R3A-, PR9, P+R9R10A-, or P(O)R;

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heteroaryl are optionally substituted with one or more so₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO2, CO₂R¹³, CN, OM, groups selected from the group consisting of alkyl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, P(0)R13R14, P+R13R14R15A-, P(0R13)OR14, S+R13R14Awherein quaternary heterocycle and quaternary naloalkyl, cycloalkyl, heterocycle, arylalkyl, ${
m so_2om},\ {
m so_2nr^{13}r^{14}},\ {
m c(0)}\ {
m nr^{13}r^{14}},\ {
m c(0)}\ {
m om},\ {
m cor^{13}},$ alkenyl, alkynyl, polyalkyl, polyether, aryl, and N+R9R11R12A-,

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OH, or SH and when R^5 is OH, R^1 , R^2 , R^3 , R^4 , R^7 and R^8 provided that both ${ t R}^5$ and ${ t R}^6$ cannot be hydrogen, cannot be all hydrogen;

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provided that when R' or R' is phenyl, only one of R or R is H;

provided that when q = 1 and R^X is styryl,

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anilido, or anilinocarbonyl, only one of \mathbb{R}^5 or \mathbb{R}^6 is alkyl;

provided that when n is 1, R¹, R³, R⁷, and R⁸ are hydrogen, R² is hydrogen, alkyl or aryl, R⁴ is unsubstituted amino or amino substituted with one or more alkyl or aryl radicals, and R⁵ is hydrogen, alkyl or aryl, then R⁶ is other than hydroxy; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferably, R⁵ and R⁶ can independently be selected from the group consisting of H, aryl, heterocycle, quaternary heterocycle, and quaternary heteroaryl,

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wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, oR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₂R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, NR¹³C(O)R¹⁴, NR¹³SOR¹⁴, NR¹³SO₂R¹⁴, NR¹³SO₂R¹⁴, NR¹³SO₂R¹⁴, NR¹³SO₂R¹⁴, NR¹³SO₂R¹⁴, NR¹³SO₂R¹⁴, NR¹³SO₂R¹⁴, OC(O)R¹³, NR¹³SO₂NR¹⁴R¹⁵, P(O)R¹³R¹⁴, P*R¹³R¹⁴R15A-, P(OR¹⁾OR¹⁴, S+R¹³R¹⁴R15A-, and N*R⁹R¹¹R¹²A⁻,

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wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR 7 , N $^+$ R 7 R 8 A-, S, SO, SO2, S $^+$ R 7 A-, PR 7 ,

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 $P(0)R^7$, $P^+R^7R^8A$ -, or phenylene,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO2R⁷, SO3R⁷, CO2R⁷, CN, oxo, CONR⁷R⁸, N⁺R⁷R⁸R⁹A⁻, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, quaternary heterocycle, and P(O) (OR⁷)OR⁸.

More preferably, R^5 or R^6 has the formula:

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-Ar-(RY) t

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t is an integer from 0 to 5;

Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; and

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one or more RY are independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)MR¹³R¹⁴, NR¹³C(O)MR¹³R¹⁴, C(O)MR¹³R¹⁴, C(O)MR¹⁴R¹⁵,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, CO2R⁷, CN, OXO, CONR⁷R⁸, N⁺R⁷R⁸R⁹A-, alkyl, alkenyl, consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, more substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, polyether, aryl, haloalkyl, cycloalkyl, and

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replaced by O, NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7 wherein said alkyl, alkenyl, alkynyl, polyalkyl, heterocycle can optionally have one or more carbons polyether, aryl, haloalkyl, cycloalkyl, and P(0)R7R8, P*R7R8A°, and P(0) (OR')OR", and P(O)R', P'R'RBA-, or phenylene.

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Still more preferably, R⁵ or R⁶ has the formula 20

(11)

A first class of compounds of particular interest consists of those compounds of formula I wherein

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q is 1 or 2;

n is 2;

R' and R' are each alkyl;

R' is hydroxy;

R' and R' are hydrogen;

'n

R' has the formula (II)

(11)

wherein t is an integer from 0 to 5;

one or more R' are OR¹³;

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nydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, urylalkyl, alkylarylalkyl, cycloalkyl, heterocycle, \mathbb{R}^{13} is selected from the group consisting of heteroaryl, quaternary heterocycle, quaternary heteroaryl, and quaternary heteroarylalkyl;

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heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR', N'R'R1'A, S, SO, carbohydrate, amino acid, peptide, or polypeptide; gaid R¹³ alkyl, alkenyl, alkynyl, arylalkyl, SO₂, S'R'A', PR', P'R'R¹⁰A', P(O)R', phenylene,

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So,R', oxo, CO,R', CN, halogen, CONR'R'', SO,OM, SO,NR'R'' heteroaryl, OR', NR'R'', N'R'R''R''A', SR', S(O)R', SO₁R', R¹³ is optionally substituted with one or more sulfoalkyl, quaternary heterocycle, quaternary groups selected from the group consisting of

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wherein A' is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation, PO(OR15)OR17, P'R'R19R11A', S'R'R10A', and C(O)OM,

R' and R' are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

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cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkenylalkyl, arylalkyl, arylalkyl, arboalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cycloalkyl, cyanoalkyl, OR*, NR*R¹⁰, SR*, S(O)R*, SO,R*, SO,R*, CO,R*, CN, halogen, oxo, and CONR*R¹⁰, wherein R* and R* cannot be defined above, provided that both R³ and R* cannot be OH, NH₂, and SH; or

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 R^{11} and R^{17} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

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 R^{14} and R^{17} are independently selected from the substituents constituting R^{9} and $M_{\it i}$

R' and R' are hydrogen; and

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one or more R^{x} are independently selected from the group consisting of alkoxy, alkylamino and dialkylamino; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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A second class of compounds of particular interest consists of those compounds of formula I wherein

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q is an integer from 1 to 4; n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

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wherein alkyl, alkenyl, alkynyl, haloalkyl alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and

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cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of or 9 , NR 9 R 10 , N $^+$ R 9 R 10 R w A $^-$, SR 9 , S'R 9 R 10 A $^-$, P $^+$ R 9 R 10 R 11 A $^-$, S(0)R 9 , S02R 9 , S03R 9 , C02R 9 , CN, halogen, oxo, and CONR 9 R 10 ,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, or phenylene,

wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheterocycle, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

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 $\rm R^1$ and $\rm R^2$ taken together with the carbon to which they are attached form $\rm C_3$ - $\rm C_{10}$ cycloalkyl;

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R³ and R⁴ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹, wherein R¹ and R¹⁰ are as defined above; or

 $m R^3$ and $m R^4$ together form =0, =NOR¹¹, =5, =NNR¹¹ $m R^{12}$, =NR⁹, or =CR¹¹ $m R^{12}$,

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wherein R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

both R3 and R4 cannot be OH, NH,, and SH,

 \mathbb{R}^{11} and \mathbb{R}^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R⁵ is aryl substituted with one or more OR^{13a},

consisting of alkylarylalkyl, alkylheteroarylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, wherein R^{13a} is selected from the group alkylheterocyclylalkyl, heterocyclylalkyl, carboxyalkylaminocarbonylalkyl, alkylammoniumalkyl, and

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groups selected from the group consisting of hydroxy, R^{13a} is optionally substituted with one or more guanidinyl, OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, heterocycle, heteroaryl, sulfoalkyl, quaternary neterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, SO2OM, SO2NR9R10, PO(OR16)OR17, P+R9R10R11A-, amino, sulfo, carboxy, alkyl, carboxyalkyl, S+R9R10A-, and C(0)OM,

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anion and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable

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wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and $M_{\it i}$ and

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is selected from the group consisting of H, heterocycle, quaternary heterocycle, ${
m OR}^{30}$, ${
m SR}^{9}$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, S(0) R9, SO2R9, and SO3R9,

cycloalkyl, heterocycle, quaternary heterocycle, and wherein alkyl, alkenyl, alkynyl, aryl,

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SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, quaternary heteroaryl can be substituted with one or OC(0)R11, OC(0)NR11R14, NR11SOR14, NR11SO1R14, NR11SONR14R11, $NR^{13}SO_{3}NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^{+}R^{13}R^{14}R^{15}A^{-}$, $P(OR^{13})OR^{14}$, NO2, \cos^{13} , CN, OM, \cos^{20} , $\cos^{13} \sin^{14}$, C(0) $\sin^{13} \sin^{14}$, more substituent groups independently selected from quaternary heteroaryl, halogen, oxo, OR^{13} , $\mathrm{NR}^{13}\mathrm{R}^{14}$, C(0) OM, COR 13, NR 11C(0) R14, NR 11C(0) NR 14R 15, NR 11CO, R14, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkynyl, neterocycle, arylalkyl, quaternary heterocycle, S+R13R14A-, and N+R9R11R12A-,

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wherein:

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A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

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consisting of OR7, NR7R8, SR7, S(O)R7, SO2R7, SO3R7, CO2R⁷, CN, oxo, CONR⁷R⁸, N⁺R⁷R⁸R⁹A-, alkyl, alkenyl, ö alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, heterocycle can be further substituted with one nore substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, Baid alkyl, alkenyl, alkynyl, polyalkyl, 2(0) R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(0) (OR⁷) OR⁸, and polyether, aryl, haloalkyl, cycloalkyl, and

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replaced by 0, NR7, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(0)R7, P † R † A-, or phenylene, and R 13 , R 14 , and R 15 wherein said alkyl, alkenyl, alkynyl, polyalkyl, are independently selected from the group consisting neterocycle can optionally have one or more carbons of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and oolyether, aryl, arylalkyl, alkylarylalkyl,

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alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, and carboxyalkylaminocarbonylalkyl,

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wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR*, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A-, P(O)R*, phenylene,

carbohydrate, amino acid, peptide, or polypeptide, and \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are optionally substituted with

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one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, org, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²R, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂ONR⁹R¹⁰, PO (OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R¹¹R.

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wherein ${\bf R}^{16}$ and ${\bf R}^{17}$ are independently selected from the substituents constituting ${\bf R}^9$ and M; or

, $s^+R^9R^{10}A^-$, and C(0)OM,

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R" and R", together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

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R¹⁴ and R¹⁵, together with the nitrogen atom to which they are attached, form a cyclic ring; and R¹⁹ is selected from the grain consisting of

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R'' is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl,

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:

arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $m R^7$ and $m R^8$ are independently selected from the group consisting of hydrogen and alkyl; and

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one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)2R¹³, SO₃R¹³, S⁺R¹³R¹⁴A⁻, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C(O)R¹³, C(O)NR¹³R¹⁴, NR¹⁴G(O)R¹³, C(O)NR¹³R¹⁴, NR¹⁴G(O)R¹³, CO)OM, COR¹³, OR¹⁸, S(O)_nNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻, p⁺R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with oR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, po (OR¹¹) oR¹¹, p⁺R⁹R¹¹R¹²A⁻, s⁺R⁹R¹⁰A⁻, or C(0)OM, and

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wherein R¹⁸ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

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wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected

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from the group consisting of $extsf{OR}^9$, $extsf{NR}^9 extsf{R}^{10}$, $extsf{N}^+ extsf{R}^3 extsf{R}^{11} extsf{R}^{12} extsf{A}^-$, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR 9R 10, SO3R 9, SO2OM, SO2NR 9R 10, PO (OR 16) OR 17, and C(0)0M,

wherein in \mathbb{R}^{X} , one or more carbons are optionally replaced by O, NR¹³, N⁺R¹³R¹⁴A-, S, SO, SO₂, S⁺R¹³A⁻, peptide, polypeptide, carbohydrate, polyether, or pR^{13} , $p(0)R^{13}$, $p^{+}R^{13}R^{14}A$ -, phenylene, amino acid, polyalkyl,

S

wherein in said polyalkyl, phenylene, amino acid, carbons are optionally replaced by 0, ${
m NR}^9$, ${
m N}^+{
m R}^9{
m R}^1{
m O}_-$, peptide, polypeptide, and carbohydrate, one or more s, so, so2, s+R3A-, PR9, P+R9R10A-, or P(O)R';

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heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, SO3R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO2, CO2R¹³, CN, OM, halogen, oxo, OR 13 , NR 13 R 14 , SR 13 , S $_{}$ S $_{}$ O $_{}$ R 13 , S $_{}$ S $_{}$ R 13 P(0)R¹³R¹⁴, P⁺R¹³R¹⁴R¹⁵A⁻, P(0R¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, wherein quaternary heterocycle and quaternary ${
m SO_2OM}$, ${
m SO_2NR^{13}R^{14}}$, ${
m C(0)NR^{13}R^{14}}$, ${
m C(0)OM}$, ${
m COR^{13}}$, haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, and N+R9R11R12A-, or

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a pharmaceutically acceptable salt, solvate, or prodrug thereof.

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Preferred compounds in this class are compounds wherein:

consisting of alkylarylalkyl, alkylheteroarylalkyl, R134 is independently selected from the group R⁵ is phenyl substituted with OR¹³⁰;

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carboxyalkylaminocarbonylalkyl; and alkylheterocyclylalkyl, and

groups selected from the group consisting of carboxy, R114 is optionally substituted with one or more

quaternary heterocycle, quaternary heteroaryl, and

in this class are More preferred compounds compounds wherein:

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R' is phenyl substituted with OR118; R''' is alkylarylalkyl; and

groups selected from the group consisting of quaternary R^{110} is optionally substituted with one or more

heterocycle and quaternary heteroaryl.

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Still more preferred in this class are compounds wherein:

R⁵ is phenyl substituted with OR¹¹⁹;

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R110 is alkylphenylalkyl; and

groups selected from the group consisting of quaternary $R^{11\bullet}$ is optionally substituted with one or more heterocycle and quaternary heteroaryl.

A third class of compounds of particular interst consists of those compounds of formula I wherein q is an integer from 1 to 4;

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n is an integer from 0 to 2;

naloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, $\ensuremath{\text{R}}^1$ and $\ensuremath{\text{R}}^2$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, lialkylamino, alkylthio, (polyalkyl)aryl, and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

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cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of or, NR 9 R 10 , N $^+$ R 9 R 10 R w A $^-$, SR 9 , S'R * R 10 A $^-$, P $^+$ R 9 R 10 R 11 A $^-$, S(O)R 9 , SO₂R 9 , SO₃R 9 , CO₂R 9 , CN, halogen, oxo, and

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR 9 , N $^+$ R 9 R 10 A-, S, SO, SO $_2$, S $^+$ R 9 A-, p $^+$ R 9 R 10 A-, or phenylene,

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wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheterocycle, carboxyheteroaryl, carboxyheterocycle, carboxloxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

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 $\rm R^1$ and $\rm R^2$ taken together with the carbon to which they are attached form $\rm C_3\text{-}C_{10}$ cycloalkyl;

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 $\rm R^3$ and $\rm R^4$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, S(0)R^9 SO_2R^9, and SO_3R^9, wherein R^3 and R^{10} are as defined above; or

 $m R^3$ and $m R^4$ together form =0, =NOR¹¹, =S, =NNR¹¹R¹², =NR⁹, or =CR¹¹R¹²,

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wherein R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

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wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH,, and SH, or

 $_{\rm R}^{11}$ and $_{\rm R}^{12}$ together with the nitrogen or carbon atom to which they are attached form a cyclic ring; $_{\rm R}^{5}$ is aryl substituted with one or more OR $_{\rm R}^{13}$ b,

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wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheterocyclylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

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 $m R^{13b}$ is substituted with one or more groups selected from the group consisting of carboxyalkyl, heterocycle, heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, or guanidinyl, and

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R⁶ is selected from the group consisting of H. 20 alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and guaternary heterocycle, and established with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³R¹⁴, NR¹³R¹⁴, SO₂R¹³, SO₂R¹³, SO₂NN, SO₂NNR¹³R¹⁴, C(O)NR¹³R¹⁴,

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OC(O)R11, OC(O)NR11R14, NR11SOR14, NR11SO1R114, NR11SONR14R15, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^{+}R^{13}R^{14}R^{15}A^{-}$, $P(OR^{13})OR^{14}$, $c(0) om, cor^{13}, nr^{13}c(0) r^{14}, nr^{13}c(0) nr^{48}r^{13}, nr^{13}co_{2}r^{14},$ S+R13R14A-, and N+R9R11R12A-,

wherein:

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A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

consisting of OR7, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, SO₃R⁷, CO2R7, CN, oxo, CONR7R8, N*R7R8R9A-, alkyl, alkenyl, heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, more substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, P(0)R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(0) (OR⁷)OR⁸, and polyether, aryl, haloalkyl, cycloalkyl, and

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heterocycle, quaternary heteroaryl, heterocyclylalkyl, P(O)R7, P*R7R8A-, or phenylene, and R13, R14, and R15 replaced by O, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷ wherein said alkyl, alkenyl, alkynyl, polyalkyl are independently selected from the group consisting heterocycle can optionally have one or more carbons quaternary heteroarylalkyl, alkylammoniumalkyl, and of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heteroarylalkyl, quaternary heterocyclylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and polyether, aryl, arylalkyl, alkylarylalkyl,

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neterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', N'R9R10A-, S, SO, SO2 wherein alkyl, alkenyl, alkynyl, arylalkyl,

carboxyalkylaminocarbonylalkyl,

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carbohydrate, amino acid, peptide, or polypeptide, and S^{+R⁹A', PR⁹, P⁺R⁹R¹⁰A-, P(O)R', phenylene,}

 $m R^{13}, \
m R^{14}, \
m and \
m R^{15}$ are optionally substituted with one or more groups selected from the group consisting carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, of hydroxy, amino, sulfo, carboxy, alkyl, quaternary heterocyclylalkyl, quaternary

CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R¹¹A. heteroarylalkyl, guanidinyl, OR 9 , NR 9 R 10 , N $^+$ R 9 R 11 R 12 A $^-$, SR_{9}^{9} , $S(O)R_{9}^{9}$, $SO_{2}R_{9}^{9}$, oxo, $CO_{2}R_{9}^{9}$, CN, halogen,

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, S*R⁹R¹⁰A-, and C(O)OM,

heterocycle that is optionally substituted with one or wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected more radicals selected from the group consisting of R" and R", together with the nitrogen atom to which they are attached form a mono- or polycyclic from the substituents constituting R⁹ and M; or oxo, carboxy and quaternary salts; or

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 $\rm R^{14}$ and $\rm R^{15},$ together with the nitrogen atom to R10 is selected from the group consisting of which they are attached, form a cyclic ring; and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl,

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carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, carboxyheterocycle, carboalkoxyalkyl, and alkylammoniumalkyl; and

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R7 and R8 are independently selected from the group consisting of hydrogen and alkyl; and

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one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen,

 $s(0)_{n}NR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^{+}R^{9}R^{11}R^{12}A^{-}$, $C(0)NR^{13}R^{14}$, NR14C(0)R13, C(0)OM, COR^{13} , OR^{18} $\rm p^+ R^9 R^{11} R^{12} A^-$, amino acid, peptide, polypeptide, and CO_2R^{13} , CN, OM, SO2OM, SO2NR $^{13}\text{R}^{14}$, NR ^{14}C (0)R 13 ,

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quaternary heteroaryl can be further substituted with PO(OR'')OR'', P+R9R11R12A-, S+R9R10A-, or C(0)OM, and oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, OR9, NR9R10, N+R9R11R12A-, SR9, S(0)R9, SO2R9, SO3R9 haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl

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carbohydrate,

of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, wherein \mathbb{R}^{18} is selected from the group consisting

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substituted with one or more substituents selected heterocycle, and quaternary heteroaryl optionally are C(0)0M $\mathtt{CONR}^9\mathtt{R}^{10}$, $\mathtt{SO}_3\mathtt{R}^9$, $\mathtt{SO}_2\mathtt{OM}$, $\mathtt{SO}_2\mathtt{NR}^9\mathtt{R}^{10}$, $\mathtt{PO}(\mathtt{OR}^{16})\mathtt{OR}^{17}$, and , sR⁹, s(0)R⁹, sO₂R⁹, sO₃R⁹, oxo, CO₂R⁹, CN, halogen from the group consisting of OR^9 , $\mathrm{NR}^9\mathrm{R}^{10}$, $\mathrm{N}^+\mathrm{R}^9\mathrm{R}^{11}\mathrm{R}^{12}\mathrm{A}^$ heterocycle, heteroaryl, alkyl, quaternary wherein acyl, arylalkoxycarbonyl, arylalkyl,

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 pR^{13} , $p(0)R^{13}$, $p+R^{13}R^{14}A-$, phenylene, amino acid, replaced by 0, NR^{13} , $N^{+}R^{13}R^{14}A^{-}$, s, s0, s02, $S^{+}R^{13}A^{-}$ wherein in $R^{\mathbf{X}}$, one or more carbons are optionally

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peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

s, so, so₂, s⁺r⁹a-, pr⁹, p⁺r⁹r¹⁰a-, or P(0)r⁴; carbons are optionally replaced by 0, NR 9 , N $^+$ R 9 R 10 A $^-$, peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid

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groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more P(0)R13R14, P+R13R14R15A-, P(OR13)OR14, S+R13R14A-, ${\rm SO_{3}R^{13}}$, ${\rm NR^{13}OR^{14}}$, ${\rm NR^{13}NR^{14}R^{15}}$, ${\rm NO_{2}}$, ${\rm CO_{2}R^{13}}$, ${\rm CN}$, ${\rm OM_{2}}$ halogen, ∞ 0, $0R^{13}$, $NR^{13}R^{14}$, SR^{13} , $S(0)R^{13}$, $S0_2R^{13}$, haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, prodrug thereof. and N+R9R11R12A-, or ${
m SO_2OM},\ {
m SO_2NR^{13}R^{14}},\ {
m C(O)NR^{13}R^{14}},\ {
m C(O)OM},\ {
m coR^{13}}$ wherein quaternary heterocycle and quaternary a pharmaceutically acceptable salt, solvate, or

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wherein: Preferred compounds in this class are compounds

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quaternary heterocyclylalkyl; and consisting of alkyl, quaternary heteroarylalkyl, and R^s is phenyl substituted with OR^{115} ; Rush is independently selected from the group

heteroaryl, and guanidinyl. selected from the group consisting of heterocycle Rib is substituted with one or more groups

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90 consists of those compounds of formula I wherein q is an integer from 1 to 4; A fourth class of compounds of particular interest ${\ensuremath{\mathbb{R}}}^1$ and ${\ensuremath{\mathbb{R}}}^2$ are independently selected from the n is an integer from 0 to 2;

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group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N*R⁹R¹⁰R*M⁴, SR⁹, S'R*R''A. P[†]R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, Oxo, and CONR⁹R¹⁰,

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wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR, N+R9R¹⁰A-, S, SO, SO₂, S⁺R⁹A[,] p⁺R⁹R¹⁰A[,] or phenylene,

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wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheterocycle, carboakyl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

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 R^{1} and R^{2} taken together with the carbon to which they are attached form $C_{1}\text{-}C_{10}$ cycloalkyl;

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R³ and R⁴ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, and SO₃R⁹, wherein R⁹ and R¹⁰ are as defined above; or

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 $\rm R^3$ and $\rm R^4$ together form =0, =NOR 11 , =5, =NNR $^{11}\rm R^{12}$, =NNR 9 , or =CR $^{11}\rm R^{12}$,

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wherein R¹¹ and R¹² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl,

cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_2R^9 , CO_2R^9 , CN, halogen, OXO, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH, and SH, or

 $\rm R^{11}$ and $\rm R^{12}$ together with the nitrogen or carbon atom to which they are attached form a cyclic ring; $\rm R^5$ is aryl substituted with one or more $\rm OR^{13b}$,

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wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heterocyclylalkyl, heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl,

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alkylammoniumalkyl, and carboxyalkyl,

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R^{13b} is substituted with one or more groups selected from the group consisting of OR^{9a}, NR^{9a}R¹⁰, N⁺R^{9a}R¹¹R¹²A⁻, SR^{9a}, S(0)R^{9a}, SO₂R^{9a}, SO₂R^{9a}, CO₂R^{9a}, C

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

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wherein R^{9a} is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino and carboxyalkylaminoalkyl;

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 $S(0)R^9$, SO_2R^9 , and SO_3R^9 , heterocycle, quaternary heterocycle, OR^{30} , SR^9 , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, ${\tt R}^{\sf G}$ is selected from the group consisting of H,

quaternary heteroaryl can be substituted with one or cycloalkyl, heterocycle, quaternary heterocycle, and C(0)OM, COR^{13} , $NR^{13}C(0)R^{14}$, $NR^{13}C(0)NR^{4}R^{15}$, $NR^{13}CO_2R^{14}$, $_{\rm SR}^{13}$, $_{\rm S(0)R}^{13}$, $_{\rm SO_2R}^{13}$, $_{\rm SO_3R}^{13}$, $_{\rm NR}^{13}{}_{\rm OR}^{14}$, $_{\rm NR}^{13}{}_{\rm NR}^{14}{}_{\rm R}^{15}$ quaternary heteroaryl, halogen, oxo, OR¹³, NR¹³R¹⁴, heterocycle, arylalkyl, quaternary heterocycle, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkynyl, more substituent groups independently selected from NR1304NR14R15, P(0)R13R14, P+R13R14R15A-, P(OR13)OR14 OC (O) R13, OC (O) NR13R14, NR13SOR14, NR13SO₂R14, NR13SONR14R15 $s^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, $_{
m NO_2}$, $_{
m CO_2R^{13}}$, $_{
m CN}$, $_{
m OM}$, $_{
m SO_2OM}$, $_{
m SO_2NR^{13}R^{14}}$, $_{
m C(O)NR^{13}R^{14}}$ wherein alkyl, alkenyl, alkynyl, aryl,

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more substituent groups selected from the group heterocycle can be further substituted with one or polyether, aryl, haloalkyl, cycloalkyl, and is a pharmaceutically acceptable cation, CO_2R^7 , CN, oxo, CONR^7R^8 , $\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}$ -, alkyl, alkenyl, consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 $P(0)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(0)(0R^7)OR^8$, and alkymyl, aryl, cycloalkyl, heterocycle, arylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and quaternary heterocycle, quaternary heteroaryl, \mathtt{A}^- is a pharmaceutically acceptable anion and M said alkyl, alkenyl, alkynyl, polyalkyl wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, $P(0)R^7$, $P^{\dagger}R^7R^8A^{-}$, or phenylene, and R^{13} , R^{14} , and R^{15} replaced by 0, NR^7 , $N^+R^7R^8A^-$, S, SO, SO2, $S^+R^7A^-$, PR^7 carboxyalkylaminocarbonylalkyl, alkylammoniumalkyl, and quaternary heteroarylalkyl, alkoxyalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary alkylheteroarylalkyl, alkylheterocyclylalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, are independently selected from the group consisting heterocycle can optionally have one or more carbons heteroarylalkyl, quaternary heterocyclylalkyl, heterocycle, quaternary heteroaryl, heterocyclylalkyl,

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heterocycle, and polyalkyl optionally have one or more carbohydrate, amino acid, peptide, or polypeptide, and $S^{+}R^{9}A^{-}$, PR^{9} , $P^{+}R^{9}R^{10}A^{-}$, $P(0)R^{9}$, phenylene, carbons replaced by 0, NR, N $^{+}$ R, N $^{+}$ R 10 A-, S, SO, SO2, wherein alkyl, alkenyl, alkynyl, arylalkyl,

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20 25 carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl one or more groups selected from the group consisting heteroarylalkyl, guanidinyl, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^$ quaternary heterocyclylalkyl, quaternary quaternary heterocycle, quaternary heteroaryl, of hydroxy, amino, sulfo, carboxy, alkyl, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO (OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R¹¹A-, sR⁹, s(0)R⁹, sO₂R⁹, sO₃R⁹, oxo, CO₂R⁹, CN, halogen, $_{
m R}^{13}$, $_{
m R}^{14}$, and $_{
m R}^{15}$ are optionally substituted with

30 which they are attached form a mono- or polycyclic from the substituents constituting R^9 and M; or R^{13} and R^{14} , together with the nitrogen atom to wherein $\mathbf{R}^{\mathbf{16}}$ and $\mathbf{R}^{\mathbf{17}}$ are independently selected

 $s^+R^9R^{10}A^-$, and C(0)OM,

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 \mathbb{R}^{14} and \mathbb{R}^{15} , together with the nitrogen atom to R¹⁰ is selected from the group consisting of which they are attached, form a cyclic ring; and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl,

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R7 and R8 are independently selected from the group consisting of hydrogen and alkyl; and

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carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl,

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and alkylammoniumalkyl; and

p*R9R11R12A, amino acid, peptide, polypeptide, and one or more $R^{\mathbf{X}}$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, heteroaryl, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, $\text{S}(\text{O})^2\text{R}^{13}$, haloalkyl, cycloalkyl, heterocycle, heteroaryl, SO3R¹³, S⁺R¹³R¹⁴A-, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, polyether, quaternary heterocycle, quaternary \cos^{13} , CN, OM, \cos_2 OM, \cos_2 NR 13 R 14 , NR 14 C(O)R 13 , $c(0)NR^{13}R^{14}$, $NR^{14}C(0)R13$, c(0)OM, COR^{13} , OR^{18} , polyalkyl, acyloxy, aryl, arylalkyl, halogen, S(0) NR18, NR13R18, NR18OR14, N*R9R11R12A-,

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quaternary heteroary) can be further substituted with OR9, NR9R10, N⁺R9R11R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, carbohydrate,

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PO(OR'*)OR'1, P'R9R11R12A-, S'R9R10A-, or C(O)OM, and

wherein R¹⁸ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

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from the group consisting of OR 9 , NR 9 R 10 , N $^+$ R 9 R 1 IR 1 2 A , SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, heterocycle, and quaternary heteroaryl optionally are $\mathrm{CONR}^9\mathrm{R}^{10}$, $\mathrm{SO}_3\mathrm{R}^9$, $\mathrm{SO}_2\mathrm{OM}$, $\mathrm{SO}_2\mathrm{NR}^9\mathrm{R}^{10}$, $\mathrm{PO}\left(\mathrm{OR}^{16}\right)\mathrm{OR}^{17}$, and substituted with one or more substituents selected wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary C(0)0M,

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wherein in RX, one or more carbons are optionally replaced by O, NR¹³, N⁺R¹³R¹⁴A⁻, S, SO, SO₂, S⁺R¹³A⁻ peptide, polypeptide, carbohydrate, polyether, or PR^{13} , $P(0)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, polyalkyl,

13

wherein in said polyalkyl, phenylene, amino acid, carbons are optionally replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, peptide, polypeptide, and carbohydrate, one or more s, so, so2, s+R3A-, PR3, P+R3R10A-, or P(O)R3;

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heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, 13 13 , 13 14 , 13 , 13 , 13 , 13 , 13 , 13 , 13 503R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, wherein quaternary heterocycle and quaternary P(0)R13R14, P+R13R14R15A-, P(0R13)OR14, S+R13R14A- ${
m SO_2OM}$, ${
m SO_2NR^{13}R^{14}}$, ${
m C(O)\,NR^{13}R^{14}}$, ${
m C(O)\,OM}$, ${
m COR^{13}}$, naloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, and N+R9R11R12A-, or

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prodrug thereof. a pharmaceutically acceptable salt, solvate, or

Preferred compounds in this class are compounds

R's is phenyl substituted with OR315

S

and alkoxyalkyl; and RIJ is substituted with one or more

selected from the group consisting of OR" and NR"R";

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carboxyalkyl, carboxyheteroaryl,

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consists of those compounds of formula I wherein

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group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

 $s(0)R^9$, so_2R^9 , so_3R^9 , co_2R^9 , CN, halogen, oxo, and OR9, NR9R10, N*R9R10RWA-, SR9, S*R*R*YA-. P*R9R10R11Asubstituents selected from the group consisting of cycloalkyl optionally are substituted with one or more dialkylamino, alkylthio, (polyalkyl)aryl, and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, wherein alkyl, alkenyl, alkynyl, haloalkyl

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wherein alkyl, alkenyl, alkynyl, alkylaryl,

carboxyheterocycle; and R^{lib} is selected from the group consisting of alkyl A fifth class of compounds of particular interest R10 is carboxyalkyl. R^{94} is selected from the group consisting of groups

n is an integer from 0 to 2; q is an integer from 1 to 4; $\ensuremath{\text{R}}^1$ and $\ensuremath{\text{R}}^2$ are independently selected from the

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alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl

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NR9, N+R9R10A-, S, SO, SO2, S+R9A-, P+R9R10A-, or phenylene, optionally have one or more carbons replaced by O,

heterocyclylalkyl, and alkylammoniumalkyl; or carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyheteroaryl, carboxyheterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, selected from the group consisting of H, alkyl, wherein R^9 , R^{10} , and R^W are independently

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they are attached form C,-C10 cycloalkyl; ${\mathbb R}^1$ and ${\mathbb R}^2$ taken together with the carbon to which

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group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, oR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, above; or $\mathrm{SO_2R}^9$, and $\mathrm{SO_3R}^9$, wherein R' and R'' are as defined $\ensuremath{\mathbb{R}}^3$ and $\ensuremath{\mathbb{R}}^4$ are independently selected from the

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=NNR¹¹R¹², =NR⁹, or =CR¹¹R¹², ${
m R}^3$ and ${
m R}^4$ together form =0, =NOR 11 , =S.

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alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, both R³ and R⁴ cannot be OH, NH₂, and SH, or $\mathrm{SO_2R}^9$, $\mathrm{SO_3R}^9$, $\mathrm{CO_2R}^9$, CN, halogen, oxo, and $\mathrm{CONR}^9\mathrm{R}^{10}$, cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹ heterocycle, carboxyalkyl, carboalkoxyalkyl, from the group consisting of H, alkyl, alkenyl wherein R^9 and R^{10} are as defined above, provided that wherein \mathbb{R}^{11} and \mathbb{R}^{12} are independently selected

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atom to which they are attached form a cyclic ring; ${\tt R}^{\sf 5}$ is aryl substituted with one or more ${\tt OR}^{\sf 13b}$ wherein R^{13b} is selected from the group and R¹² together with the nitrogen or carbon

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S

heterocycle, quaternary heteroaryl, heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and heteroarylalkyl, quaternary heterocyclylalkyl, carboxyalkylaminocarbonylalkyl,

R^{13b} is substituted with one or more groups carboxyalkylheterocyclyl, ${
m NR}^9{
m R}^{10a}$, ${
m CONR}^9{
m R}^{10a}$ SO2NR9R10a, P+R9R10aR11A-, and S+R9R10aA-, selected from the group consisting of

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anion and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable

consisting of carboxyalkyl, carboalkoxyalkyl, wherein R^{10a} is selected from the group carboxyalkylamino, heteroarylalkyl, and heterocyclylalkyl; or

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R⁶ is selected from the group consisting of H, heterocycle, quaternary heterocycle, ${
m OR}^{30}$, ${
m SR}^9$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, s(0)R⁹, SO₂R⁹, and SO₃R⁹,

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SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or NO2, $\cos R^{13}$, CN, ОМ, $\sin \cos NM$, $\sin \sin N^{13}R^{14}$, C(O) $\sin \sin^{13}R^{14}$, nore substituent groups independently selected from quaternary heteroaryl, halogen, oxo, OR 13 , NR 13 R 14 , polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkynyl. neterocycle, arylalkyl, quaternary heterocycle, wherein alkyl, alkenyl, alkynyl, aryl,

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OC(0)R11, OC(0)NR11R1, NR11SOR11, NR11SO1R11, NR11SONR11R11, NR13SO,NR14R15, P(O)R¹³R14, P⁺R¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴ C(0) OM, COR¹³, NR¹³C(0) R¹⁴, NR¹³C(0) NR¹⁴R¹³, NR¹³CO₂R¹⁴, S+R13R14A-, and N+R9R11R12A-,

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A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO2R7, CN, OXO, CONR7R8, N+R7R8R9A-, alkyl, alkenyl. heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, more substituent groups selected from the group said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and

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quaternary heterocycle, quaternary heteroaryl, (0) R7R8, P+R7R8R9A-, and P(0) (OR7) OR8, and

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replaced by O, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R7, P*R7R8A-, or phenylene, and R13, R14, and R15 wherein said alkyl, alkenyl, alkynyl, polyalkyl, are independently selected from the group consisting heterocycle can optionally have one or more carbons of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and polyether, aryl, arylalkyl, alkylarylalkyl,

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neterocycle, quaternary heteroaryl, heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and sycloalkyl, heterocycle, heteroaryl, quaternary neteroarylalkyl, quaternary heterocyclylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, carboxyalkylaminocarbonylalkyl,

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heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', N⁺R⁹R¹⁰A-, S, SO, SO₂, wherein alkyl, alkenyl, alkynyl, arylalkyl,

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carbohydrate, amino acid, peptide, or polypeptide, and $s^+R^9A^-$, pR^9 , $p^+R^9R^{10}A^-$, $p(0)R^9$, phenylene

of hydroxy, amino, sulfo, carboxy, alkyl, one or more groups selected from the group consisting quaternary heterocyclylalkyl, quaternary quaternary heterocycle, quaternary heteroaryl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, $\text{CONR}^2 \text{R}^{10}$, $\text{SO}_2 \text{OM}$, $\text{SO}_2 \text{NR}^2 \text{R}^{10}$, $\text{PO}(\text{OR}^{16}) \text{OR}^{17}$, $\text{P}^+ \text{R}^9 \text{R}^{10} \text{R}^{11} \text{A}$. heteroarylalkyl, guanidinyl, OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A , sR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, $m R^{13}$, $m R^{14}$, and $m R^{15}$ are optionally substituted with

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from the substituents constituting R^9 and M; or $S^{+}R^{9}R^{10}A^{-}$, and C(0)0M, wherein ${\mathbf R}^{16}$ and ${\mathbf R}^{17}$ are independently selected

more radicals selected from the group consisting of heterocycle that is optionally substituted with one or which they are attached form a mono- or polycyclic oxo, carboxy and quaternary salts; or R^{13} and R^{14} , together with the nitrogen atom to

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carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, carboxyheterocycle, carboalkoxyalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, which they are attached, form a cyclic ring; and and alkylammoniumalkyl; and R10 is selected from the group consisting of ${
m R}^{14}$ and ${
m R}^{15}$, together with the nitrogen atom to

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group consisting of hydrogen and alkyl; and $\ensuremath{\text{R}}^7$ and $\ensuremath{\text{R}}^8$ are independently selected from the

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the group consisting of H, alkyl, alkenyl, alkynyl polyalkyl, acyloxy, aryl, arylalkyl, halogen, one or more $R^{\mathbf{X}}$ are independently selected from

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heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$ polyether, quaternary heterocycle, quaternary $_{\rm P}^{+}{}_{\rm R}^{9}{}_{\rm R}^{11}{}_{\rm R}^{12}{}_{\rm A}^{-}$, amino acid, peptide, polypeptide, and S(0)nNR18, NR13R18, NR18OR14, N+R9R11R12A- $C(0)NR^{13}R^{14}$, NR14C(0)R13, C(0)OM, COR^{13} , OR^{18} ${\rm CO_2R^{13}}$, CN, OM, ${\rm SO_2OM}$, ${\rm SO_2NR^{13}R^{14}}$, ${\rm NR^{16}C(0)R^{13}}$, $503R^{13}$, $S^{+}R^{13}R^{14}A^{-}$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , haloalkyl, cycloalkyl, heterocycle, heteroaryl carbohydrate,

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exo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$ OR9, NR9R10, N+R9R11R12A-, SR9, S(O)R9, SO2R9, SO3R9 quaternary heteroaryl can be further substituted with haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, $PO(OR^{14})OR^{17}$, $P^{+}R^{9}R^{11}R^{12}A^{-}$, $S^{+}R^{9}R^{10}A^{-}$, or C(0)OM, and wherein alkyl, alkenyl, alkynyl, cycloalkyl, wherein R^{18} is selected from the group consisting

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of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, wherein acyl, arylalkoxycarbonyl, arylalkyl,

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 $\text{CONR}^9\text{R}^{10}$, SO_3R^9 , SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}\left(\text{OR}^{16}\right)\text{OR}^{17}$, and , SR^9 , $S(0)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, from the group consisting of OR 9 , NR $^9\mathrm{R}^{10}$, N $^+\mathrm{R}^9\mathrm{R}^{11}\mathrm{R}^{12}\mathrm{A}^$ substituted with one or more substituents selected heterocycle, and quaternary heteroaryl optionally are heterocycle, heteroaryl, alkyl, quaternary

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 pR^{13} , $p(0)R^{13}$, $p+R^{13}R^{14}A$ -, phenylene, amino acid, replaced by O, NR^{13} , $N^{\dagger}R^{13}R^{14}A$ -, S, SO, wherein in $R^{\mathbf{X}}$, one or more carbons are optionally so2, s+R13A-,

wherein in said polyalkyl, phenylene, amino acid,

carbons are optionally replaced by 0, ${\rm NR}^9$, ${\rm N}^+{\rm S}_{\rm R}^{\rm 10}{\rm A}^{\rm -}$ peptide, polypeptide, and carbohydrate, one or more

s, so, so₂, $s^+ R^9 A$ -, PR^9 , $P^+ R^9 R^{10} A$ -, or $P(0)R^9$;

heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, wherein quaternary heterocycle and quaternary halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl,

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SO3R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM,

 ${
m SO}_2{
m OM},~{
m SO}_2{
m NR}^{13}{
m R}^{14},~{
m C(0)}\,{
m NR}^{13}{
m R}^{14},~{
m C(0)}\,{
m OM},~{
m COR}^{13},$

P(0)R¹³R¹⁴, P+R¹³R¹⁴R¹⁵A⁻, POR¹³OR¹⁴, S+R¹³R¹⁴A⁻,

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and N+R9R11R12A-, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof. Preferred compounds in this class are compounds

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R° is phenyl substituted with OR¹¹⁵; wherein:

R is alkyl; and

R^{11b} is substituted with NR'R^{10a}; and R' is hydrogen; and

R10 is heteroarylalkyl.

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A sixth class of compounds of particular interest consists of those compounds of formula I wherein

q is an integer from 1 to 4; n is an integer from 0 to 2;

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group consisting of H, alkyl, alkenyl, alkynyl

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 \mathbb{R}^1 and \mathbb{R}^2 are independently selected from the

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haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

cycloalkyl optionally are substituted with one or more OR9, NR9R10, N'R9R10RWA-, SR9, S'R'R10A. P'R9R10R11Asubstituents selected from the group consisting of S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and wherein alkyl, alkenyl, alkynyl, haloalkyl dialkylamino, alkylthio, (polyalkyl) aryl, and alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, CONR9R10

alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR9, N+R9R10A-, S, SO, SO2, S+R9A', P+R9R10A', or wherein alkyl, alkenyl, alkynyl, alkylaryl, phenylene,

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alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of H, alkyl, ammoniumalkyl, arylalkyl, carboxyalkyl,

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carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, neterocyclylalkyl, and alkylammoniumalkyl; or carboxyheteroaryl, carboxyheterocycle,

 R^1 and R^2 taken together with the carbon to which

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acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, R³ and R⁴ are independently selected from the ${
m SO}_2{
m R}^9$, and ${
m SO}_3{
m R}^9$, wherein ${
m R}^9$ and ${
m R}^{10}$ are as defined group consisting of H, alkyl, alkenyl, alkynyl, they are attached form C,-C,, cycloalkyl;

R³ and R⁴ together form =0, =NOR¹¹, =S, "NNR¹¹R¹², "NR⁹, or "CR¹¹R¹²,

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alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, from the group consisting of H, alkyl, alkenyl, wherein R^{11} and R^{12} are independently selected

cycloalkyl, cyanoalkyl, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, $\mathrm{SO_2R^9}$, $\mathrm{SO_3R^9}$, $\mathrm{CO_2R^9}$, CN, halogen, oxo, and $\mathrm{CONR^9R^{10}}$ wherein R^9 and R^{10} are as defined above, provided that both R³ and R⁴ cannot be OH, NH₃, and SH, or

atom to which they are attached form a cyclic ring; \mathbb{R}^{11} and \mathbb{R}^{12} together with the nitrogen or carbon

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NR11SONR14R15, and NR11SO,NR14R15, NR13CO,R14, OC (O) R13, OC (O) NR13R14, NR13SOR14, NR13SO,R14, group consisting of NR11C(O)R11, NR11C(O)NR14R15 substituent groups independently selected from the R⁵ is aryl substituted with one or more

wherein:

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alkylarylalkyl, alkylheteroarylalkyl, the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, carboxyalkylaminocarbonylalkyl, heteroarylalkyl, alkylammoniumalkyl, and quaternary heterocyclylalkyl, quaternary heteroaryl, heterocyclylalkyl, heteroarylalkyl heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle R^{13} , R^{14} , and R^{15} are independently selected from

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of hydroxy, amino, sulfo, carboxy, alkyl, one or more groups selected from the group consisting heteroarylalkyl, guanidinyl, OR^9 , NR^9R^{10} , $N^{\dagger}R^9R^{11}R^{12}A^{-}$ quaternary heterocyclylalkyl, quaternary quaternary heterocycle, quaternary heteroaryl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, ${\mathbb R}^{13}$, ${\mathbb R}^{14}$, and ${\mathbb R}^{15}$ are optionally substituted with

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, sR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen,

 $\text{CONR}^9 \text{R}^{10}$, $\text{SO}_2 \text{OM}$, $\text{SO}_2 \text{NR}^9 \text{R}^{10}$, $\text{PO} (\text{OR}^{16}) \text{OR}^{17}$, $\text{p}^+ \text{R}^9 \text{R}^{10} \text{R}^{11} \text{A}$ $s^+R^9R^{10}A^-$, and C(0)0M,

oxo, carboxy and quaternary salts; or from the substituents constituting R^9 and M; or anion and M is a pharmaceutically acceptable cation, heterocycle that is optionally substituted with one or which they are attached form a mono- or polycyclic more radicals selected from the group consisting of wherein A is an pharmaceutically acceptable R^{13} and $R^{14},\ \text{together}$ with the nitrogen atom to wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected

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which they are attached, form a cyclic ring; and R^{14} and R^{15} , o, together with the nitrogen atom to

s(0)R9, s02R9, and s03R9, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, \mathbb{R}^6 is selected from the group consisting of H,

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30 $_{\rm SR}^{13}$, $_{\rm S(0)R}^{13}$, $_{\rm SO_2R}^{13}$, $_{\rm SO_3R}^{13}$, $_{\rm NR}^{13}$ $_{\rm OR}^{14}$, $_{\rm NR}^{13}$ $_{\rm NR}^{14}$ $_{\rm R}^{15}$ quaternary heteroaryl, halogen, oxo, OR13, NR13R14, heterocycle, arylalkyl, quaternary heterocycle, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, the group consisting of alkyl, alkenyl, alkynyl, more substituent groups independently selected from quaternary heteroaryl can be substituted with one or cycloalkyl, heterocycle, quaternary heterocycle, and OC(0)R11, OC(0)NR11R14, NR11SOR14, NR11SO₂R14, NR11SONR14R15 C(0)OM, COR^{13} , $NR^{13}C(0)R^{14}$, $NR^{13}C(0)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $NR^{11}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^{+}R^{13}R^{14}R^{15}A^{-}$, $P(OR^{13})OR^{14}$ $_{
m NO_2}$, $_{
m CO_2R^{13}}$, $_{
m CN}$, $_{
m OM}$, $_{
m SO_2OM}$, $_{
m SO_2NR^{13}R^{14}}$, $_{
m C}$ (0) $_{
m NR^{13}R^{14}}$ wherein alkyl, alkenyl, alkynyl, aryl,

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S+R13R14A-, and N+R9R11R12A-

A is a pharmaceutically acceptable anion and M said alkyl, alkenyl, alkynyl, polyalkyl, is a pharmaceutically acceptable cation,

consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO2R⁷, CN, oxo, CONR⁷R⁸, N⁺R⁷R⁸R⁹A-, alkyl, alkenyl, heterocycle can be further substituted with one or alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, more substituent groups selected from the group quaternary heterocycle, quaternary heteroaryl, P(0) R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(0) (OR⁷) OR⁸, and polyether, aryl, haloalkyl, cycloalkyl, and

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heterocycle, quaternary heteroaryl, heterocyclylalkyl, replaced by 0, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(0)R7, P R7R8A-, or phenylene, and R13, R14, and R15 wherein said alkyl, alkenyl, alkynyl, polyalkyl, are independently selected from the group consisting heterocycle can optionally have one or more carbons quaternary heteroarylalkyl, alkylammoniumalkyl, and of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heteroarylalkyl, quaternary heterocyclylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and polyether, aryl, arylalkyl, alkylarylalkyl, carboxyalkylaminocarbonylalkyl,

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carbohydrate, amino acid, peptide, or polypeptide, and R¹³, R¹⁴, and R¹⁵ are optionally substituted with heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', N'R'R'D'A-, S, SO, SO2, wherein alkyl, alkenyl, alkynyl, arylalkyl, S*R9A', PR9, P*R9R10A-, P(O)R', phenylene,

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heteroarylalkyl, guanidinyl, OR 9 , NR 9 R 10 , N $^+$ R 9 R 11 R 12 A $^$ one or more groups selected from the group consisting , $\rm SR^9$, $\rm S(0)R^9$, $\rm SO_2R^9$, $\rm oxo$, $\rm CO_2R^9$, CN, halogen, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, of hydroxy, amino, sulfo, carboxy, alkyl quaternary heterocyclylalkyl, quaternary

 $\cos R^9 R^{10}$, $\cos_2 \cos N$, $\cos_2 N R^9 R^{10}$, $\cos (\cos R^{16}) \cos R^{17}$, $p^+ R^9 R^{10} R^{11} A^{-1}$, S*R9R10A-, and C(0) OM,

heterocycle that is optionally substituted with one or more radicals selected from the group consisting of wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected R13 and R14, together with the nitrogen atom to which they are attached form a mono- or polycyclic from the substituents constituting R^9 and M; or oxo, carboxy and quaternary salts; or

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carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl $R^{14}\ _{and}\ R^{15},$ together with the nitrogen atom to R10 is selected from the group consisting of which they are attached, form a cyclic ring; and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, and alkylammoniumalkyl; and

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 \mathbb{R}^7 and \mathbb{R}^8 are independently selected from the group consisting of hydrogen and alkyl; and

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one or more \mathbb{R}^{X} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, neteroaryl, ${
m OR}^{13}$, ${
m NR}^{13}{
m R}^{14}$, ${
m SR}^{13}$, ${
m S}({
m O}){
m R}^{13}$, ${
m S}({
m O}){
m 2R}^{13}$, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary polyalkyl, acyloxy, aryl, arylalkyl, halogen,

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 $S(O)_{D}NR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^{+}R^{9}R^{11}R^{12}A^{-}$, $C(O)NR^{13}R^{14}$, NR14C(O)R13, C(O)OM, COR^{13} , OR^{18} , CO2R13, CN, OM, SO2OM, SO2NR13R14, NR14C(O)R11 SO3R13, S+R13R14A-, NR13OR14, NR13NR14R15, NO2,

 $\mathfrak{p}^{+}\mathfrak{R}^{9}\mathfrak{R}^{11}\mathfrak{R}^{12}\mathfrak{A}^{-}$, amino acid, peptide, polypeptide, and carbohydrate,

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OR9, NR9R10, N+R9R11R12A-, SR9, S(O)R9, SO2R9, SO3R9, $PO(OR^{16})OR^{17}$, $P^{\dagger}R^{9}R^{11}R^{12}A^{-}$, $S^{\dagger}R^{9}R^{10}A^{-}$, or C(0)OM, and oxo, CO2R9, CN, halogen, CONR9R10, SO2OM, SO2NR9R10 quaternary heteroaryl can be further substituted with haloalkyl, polyether, quaternary heterocycle, and aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl,

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of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein R^{18} is selected from the group consisting

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heterocycle, and quaternary heteroaryl optionally are heterocycle, heteroaryl, alkyl, quaternary wherein acyl, arylalkoxycarbonyl, arylalkyl,

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, SR^9 , $S(0)R^9$, SO_2R^9 , SO_3R^9 , SN, SNCONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$

peptide, polypeptide, carbohydrate, polyether, or replaced by 0, $m NR^{13}$, $m N^{\dagger}R^{13}R^{14}A^{-}$, S, S0, S02, $m S^{\dagger}R^{13}A^{-}$, , $P(0)R^{13}$, $p^+R^{13}R^{14}A^-$, phenylene, amino acid, wherein in Rx, one or more carbons are optionally

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peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid,

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s, so, so₂, s[†]R⁹A-, PR⁹, P[†]R⁹R¹⁰A-, or P(0)R*; carbons are optionally replaced by 0, NR 9 , N $^+$ R 9 R 10 A $^-$,

and N+R9R11R12A-, or P(0)R13R14, P+R13R14R15A-, P(OR13)OR14, S+R13R14A- SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13} SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, halogen, ∞ o, $0R^{13}$, $NR^{13}R^{14}$, SR^{13} , $S(0)R^{13}$, SO_2R^{13} haloalkyl, cycloalkyl, heterocycle, arylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

prodrug thereof. a pharmaceutically acceptable salt, solvate, or

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wherein: Preferred compounds in this class are compounds

from the group consisting of NR13C(0)NR14R15 and NR14CO2R14. R is aryl substituted with a radical selected

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compounds wherein: More preferred compounds In this class are

from the group consisting of NR13C(0)NR14R13 and NR13CO,R11. R' is phenyl substituted with a radical selected

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the following conditions exist: the above embodiments, wherein at least one or more of directed to compounds of Formula I, including each of Other embodiments of the invention are further

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group consisting of hydrogen and alkyl. Preferably, R consisting of $C_{1-\epsilon}$ alkyl. More preferably, R^{ϵ} and R^{2} are and R' are independently selected from the group the same C_{i.,} alkyl. (1) R1 and R2 are independently selected from the Still more preferably, R' and R'

concentrated in vacuo gave a white solid (0.349g/45%). silica gel eluting with 30% ethyl acetate/hexane and After 24 hours, dichloromethane (75.0 mL) was added. іл vacuo. aqueous NaCl (25.0 mL), dried (MgSO,), and concentrated The mixture was washed with aqueous NaHCO; (25.0 mL), sulfonamoyl chloride (0.181g/0.628 mmol) were added Purification by flash chromatography on

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4.24 (m, 9H), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), .2.81 (s, 6H), 3.09 (dd, J = 36.6, 15.3 Hz; 2H), 4.11-Calc'd for C34H52N3O9S2: 710.3145. Found: 710.3158 6.51 (dd, J = 8.7, 2.4 Hz, 1H), 7.24-7.38 (m, 5H), 7.44 1.27 (t, J = 7.2 Hz, 6H), 1.90 (m, 1H), 2.21 (m, 1H), (bs, 1H), 7.90 (d, J = 9.0 Hz, 1H). HRMS (ESI/M + H). 1H NMR (CDCl3) & 0.91 (m, 6H), 1.10-1.70 (m, 10H),

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Step 3: Preparation of Title Compound:

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ether gave a white crystalline solid (0.109g/53%). 1H mL), and acidified with aqueous 3.0 N HCl (0.40 mL). NMR (CD3OD) 8 0.89 (m, 6H), 1.05-1.50 (m, 10H), 1.68 concentrated in vacuo. Precipitation from After 18 hours, a white precipitate had formed, which aqueous mixture was washed with diethyl ether (4 \times 4.0 After 30 minutes, water (6.0 mL) was added. The additional LiOH.H₂O (0.015g/0.357 mmol) was added. magnetic stirrer. A solution of LiOH.H,O (0.030g/0.715 mL) were combined in a 10 mL round-bottom flask. The Example (0.224g/0.316 mmol) and tetrahydrofuran (1.00 (m, 1H), 2.16 (m, 1H), 2.89 (s, 6H), 3.13 (m, 2H), 4.07 recrystallization from t-butyl methyl ether/diethyl acetonitrile/diethyl ether/hexanes and was filtered, washed with water (2.0 mL) and mmol) in water (0.50 mL) was added. After 4 hours, reaction flask was purged with N, and equipped with 4H), 4.18 (s, 1H), 5.45 (s, 1H), 6.52 (s, 1H), 6.93 The benzothiepine prepared in step 2 of this

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+ H). Calc'd for C30H44N3O9S2: 654.2519. Found: 3H), 7.70 (bs, 1H), 7.99 (d, J = 8.7 Hz, 1H) HRMS (ESI/M (d, J = 8.7 Hz, 1H), 7.19 (d, J = 6.6 Hz, 1H), 7.35 (m,

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which is then demethylated to form the intermediate 5the synthesis. For example, where the synthesis chromatographic purification at an appropriate stage of product can be obtained by use of chiral product is desired, the enantiomeric-enriched final the above examples and an enantiomeric-enriched final non-enantioselective synthesis is employed in any of proceeds through the intermediate 5-(4'-methoxyphenyl)-7- (dimethylamino) tetrahydrobenzothiepine-1, 1-dioxide As one skilled in the art will appreciate, where a

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methoxyphenyl)-7-

tetrahydrobenzothiepine-1,1-dioxide, the 5-(4'-

(4'-hydroxyphenyl)-7-(dimethylamino)-

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preferably is subjected to a chiral chromatagraphic enantiomeric-enriched intermediate 5-(4'enantiomer is then demethylated to yield the purification step prior to demethylation. The separated (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide hydroxyphenyl)-7-

purification could be performed immediately prior use in the next step of the synthesis. By way of Chiralpak AD column with an ethanol/heptane mobile resulting in an enantiomeric-enriched final product. intermediate in Step 7 of the synthesis thereby The separated enantiomer is then used as an phase (5%-10% ethanol v/v) at a wavelength of 220 nm. Step 7 of Example 1398a using a column such as a further illustration, chiral chromatographic (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide for

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the intermediate 5-(3'-methoxyphenyl)-7-Similarly, where the synthesis proceeds through

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1H), 6.48 (d, J = 8.9 Hz, 1H), 7.33 (m, 1H), 7.70 (br s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.93 (s, 1H), 11.3 (s, 1H); HRMS. Calc'd for $C_{11}H_{11}N_{1}O_{1}S$: 611.3631. Found: 611.3638.

Example 1460

Preparation of:

Step 1: Preparation of diethyl iminodiacetatosulfonamoyl chloride

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Sulfuryl chloride (27.552g/204.1 mmol) and chloroform (50.0 mL) were combined in a 250 mL round-bottom flask. The reaction flask was purged with $N_{\rm J}$

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equipped with magnetic stirrer, and cooled to 0 °C. A solution of diethyl iminodiacetate (18.902g/99.9 mmol) and triethylamine (10.112g/99.9 mmol) was added dropwise while maintaining the temperature of the solution below 20 °C. After the addition was completed, the reaction mixture was allowed to warm to room temperature. After 2 hours, the reaction mixture was poured into ice water (100 mL) and mixed well. The organic layer was separated, washed with 10% aq. HCl (50 mL) and chilled water (2 x 50 mL), dried (CaCl₂), filtered and concentrated in vacuo to give an amber liquid (5.706g/20%). 1H NMR (CDCl₃) & 1.30 (t, 6H), 4.23 (q, 4H), 4.38 (s, 4H). HRMS (EI/M + H). Calc'd for CgHISNOGSCl: 288.0309. Found: 288.0300.

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Step 2: Preparation of:

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The 3-aminobenzothiepine of step 5 of Example 1398 (0.503g/1.097 mmol), toluene (5.00 mL), disopropylethylamine (0.148g/1.148 mmol), and the diethyl iminodiacetato-sulfonamoyl chloride prepared in step 1 of this Example (0.650g/2.260 mmol) were combined in a 25 mL round-bottom flask. The reaction flask was purged with N, and equipped with magnetic stirrer. After 18 hours, additional diisopropylethylamine (0.074g/0.574 mmol) and diethyl iminodiacetato-

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1.4 eq.), followed

by the dropwise addition of

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g of a syrup, MS (negative FAB), m/e 686 (M * -1); NMF ether and water (100 ml each). A waxy material dried (MgSO,) and concentrated in vacuum to yield 1.35 HCl and extracted with CH2Cl2. The CH3Cl2 layer was the aqueous layer and was acidified with concentrated resulted that was insoluble to both the ether and 3.7(s, 2H), 3.1-3.2 (ABq, 2H), 2.9 (s, 6H), 2.3 (t (d, 2H, 7 Hz), 6.7 (d, 1H, 7 Hz), 6.2 (s, 1H), 5.6 aqueous layers. The waxy material was combined with 2H, B Hz), 0.9-2.0 (m, 24H). (8, 1H), 5.15 (8, 2H), 4.2 (8, 1H), 4.1 (8, 2H), (CDCl₁), 8.0 (d, 1H, 7 Hz), 7.50 (d, 2H, 7 Hz), 7.00 concentrated in vacuum. The residue was stirred

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Preparation of:

azoniabicyclo[2.2.2]octane chloride benzothiepin-5-yl]]phenylacetamido]-4-aza-1-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-(4R-cis)-1-[N-[3-[3,3-Dibutyl-7-(dimethylamino)-

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dichloromethane (10 mL) at 0 °C under N, was treated Example 1398, A solution of the aniline derivative prepared in Step 5 (1.0 g, 2.2 mmol) in

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and the aqueous layer was extracted with ethyl acetate mixture was quenched by the addition of 1N HCl (25 mL)

with saturated aqueous sodium bicarbonate (2 imes 25 mL) (2 x 25 mL). The combined organic extracts were washed

dried

a 10 minute period. The reaction mixture was stirred chloroacetyl chloride (0.21 mL, 2.6 mmol, 1.2 eq.) over

and allowed to warm to 25 °C over a 2 hour period. The

Example 1459

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Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H), 8.30 (s, 1H). 8.9, 2.4 Hz, 1H), 7.37-7.49 (m, 2H), 7.79 (d, J = 8.54.23 (s, 2H), 5.57 (s, 1H), 6.05 (m, 1H), 6.58 (dd, J =

15.0 Hz, J = 48.8 Hz, 2H), 4.15 (d, J = 6.2 Hz, 1H),

yellow solid: 1 H NMR (CDCl₃) δ 0.95 (m, 6H), 1.15-1.71 chloroacetyl intermediate (0.74 g, 63%) as a pale collected and washed with hexane (50 mL) to give a

(br m, 11H), 2.24 (m, 1H), 2.85 (8, 6H), 3.12 (ABq, J =

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crystallized upon standing. concentrated to give a pale and brine (30 mL), and were

The white crystals were

yellow oil which (MgSO₄) and

with N,N-di-isopropyl-ethylamine (0.53 mL, 3.1 mmol

35 ä 25 J = 15.1 Hz, J = 34.3 Hz, 2H), 3.21 (m, 6H), 3.796H), 4.12 (8, 1H), 4.62 (8, 2H), 5.41 (8, 1H), 5.99 (m, 1.80 (br m, 4H), 2.14 (m, 1H), 2.75 (s, 6H), 3.08 (ABq, NMR (CDCl₃) & 0.88 (m, 6H), 1.08-1.42 (br m, 8H), 1.45compound (17 mg, 55%) as a white crystalline solid: 1H tert-butyl methyl ether (25 mL) to give the title resulting white solid was collected and washed with stand overnight during which time crystals formed. The methyl ether was added. was dissolved in warm acetonitrile and °C and was concentrated to form a residue. The residue mg, 0.09 mmol, 1.8 eq.) and stirred at 50 °C for 2 was treated with diazabicyclo[2.2.2]octane (DABCO, 10 mg, 0.05 mmol) in acetonitrile (1 mL) at 50 °C under N_2 A solution of the chloroacetyl intermediate (26 The reaction mixture was allowed to cool to 25 The mixture was allowed to tert-butyl

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tris(trimethylsily1) phosphite was refluxed at 100 °C overnight. The reaction mixture was cooled to room (8, 1H), 5.48 (8, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.53 temperature and 30 mL of 50% methanol/water solution for 5 hours. The mixture was concentrated in vacuo and the resulting aqueous solution was extracted with CH, Cl,. The CH, Cl, solution was dried over MgSO, and concentrated in vacuo to yield a yellowish oil. The oil was dissolved in CH,Cl, and triturated with ethyl acetate to give 202 mg of the desired product (50%) as a white solid. ¹H NMR (CDCl₃) § 0.90 (m, 6H), 1.14-2.10 (m, 21H), 2.81 (s, 6H), 3.07 (ABq, 3.98 (m, 3H), 4.11 A stirred solution of 400 mg of the bromide was added. The mixture was stirred at room temperature (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, ZH), 7.89 (d, J = 8.4 Hz, 1H). 튐 ~ mmol) 99.0) intermediate

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Example 1458

Preparation of:

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A mixture of 0.325 g (1.78 mmol) of 5mercaptotetrazoleacetic acid sodium salt, 1.0 g of potassium carbonate, and 30 ml of dimethylformamide was stirred for 2 hours then was charged with 1.06 g

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(1.74 mmol) of 5-R-[4-(5-bromopentoxy)phenyl-3,3-dibutyl-7-dimethylamino-4-R-hydoxybenzothiepine-1,1-dioxide (Example 1413, Step 1). The reaction mixture was stirred for 20 hours at room temperature and

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2H), 5.42 (s, 1H), 5.78 (s, 1H), 6.04 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 6.4, 3.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.31 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H). Mass spectroscopy data also verified desired product.

Example 1456

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Preparation of:

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and extracted with CH2Cl2 (2x50 ml). The CH2Cl2 layer was diluted with 25 ml of water and acidified to pH 2 at 45 °C for 3 days and concentrated in vacuum to 25 ml of tetrahydrofuran, and 25 ml of water was held mixture of this residue, 0.8 g of lithium hydroxide, diethyl iminodiacetate to give 1.0 g of a residue. A distilled at 0.5 torr at 120 °C to remove excess was dried (MgSO,) and concentrated in vacuum. The remove tetrahydrofuran. The residual aqueous solution concentrated in vacuum. The residue was kugelrohr diluted with brine and extracted with CH2Cl1. The CH2Cl1 1), 11.45 g of diethyl iminodiacetate, and 1.14 g of 4-R-hydroxybenzothiepine-1,1-dioxide (Example 32, Step layer was washed with brine, dried (MgSO4) and sodium carbonate was held at 160 °C for 3.5 hours, bromoethoxyethoxy)phenyl-3,3-dibutyl-7-dimethylamino-A mixture of 0.845 g (10.7 mmol) of 5-R-[4-(2-

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residual solid was dissolved in hot CH_2Cl_1 and triturated with ether. The precipitate was collected to give 0.86 g of solid, MS (negative FAB), m/e 685 (M' + Na).

Example 1457

Preparation of:

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HOOH

A solution of 500 mg of desired 5-(4'-hydroxyphenyl)-7-

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concentrated The ethyl acetate layer was dried over MgSO, and with water at 0 °C and extracted with ethyl acetate. stirred for 1 hour. The reaction mixture was quenched minutes. A solution of 1.25 g of 1,5-dibromopentane dimethylformamide at -10 °C in an acetone-dry ice bath. minutes and allowed to warm up to room temperature and added. The mixture was stirred at -10 °C for another 30 The resulting solution was stirred at -10 °C for 30 solution of 36 mg of 95% NaH (1.41 mmol) in 5 mL of dimethylformamide was added via a syringe to a stirred (5.45 mmol) in 5 mL of dimethylformamide was then (Example 1402, Step 10) (1.09 mmol)in 5 mL (dimethylamino) tetrahydrobenzothiepine-1, 1-dioxide vacuo. The crude product

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Preparation of:

1448.

1447.

1449.

The 3-aminobenzothiepine of step 5 of Example 1398 Alabama 35801), and CDC1, (0.7 mL) were combined in an 8 mm NMR tube. The tube was purged with N., After 72 nrs, the reaction mixture was heated to 50 °C. After (Methoxy-PEG-NCO, MW 5000, purchased from Shearwater (0.0165g/0.0360 mmol), M-NCO-5000 (0.150g/0.30 mmol) Polymers Inc., 2130 Memorial Parkway, SW, Huntsville,

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1450.

1451.

1452.

24 hrs, an additional aliquot of the 3-

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reaction mixture was transferred to a 2 mL vial and (0.0077g/0.017 mmol) was added. After 24 hrs, the uminobenzothiepine of step 5 of Example 1398

was repeated until no starting material was detected in precipitate and filtered. This precipitation procedure evaporated to dryness with a N, purge. The resulting white solid was dissolved in hot ethyl ether $(2.0\ \mathrm{mL})$ and ethyl acetate (0.057 mL/4 drops), cooled to the precipitate (TLC: SiO,/80% EtOAc/hexanes).

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1.05-1.49 (m, 14H), 1.18 (t, J = 6.8 Hz, 2H), 1.59 (bt, 1H), 2.18 (bt, 1H), 2.34 (s, 2H), 2.78 (s, 6H), 3.04 (ABq, 2H), 3.35-3.80 (m, 625H), 4.09 (d, J = 7.2 Hz, (0.0838g/51%). 1H NMR (CDC13) d 0.82-0.90 (m, 6H), Concentrated in vacuo to give a white solid

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Examples 1438 - 1454

application or using methods known to those skilled in synthetic schemes previously disclosed in this the art. prepared in accordance with one or more of the The compounds of Examples 1438 through 1454 can be

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Step 2.

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reflux. After 0.5 hrs, the reaction mixture was cooled lash chromatography on silica gel eluting with 20-30% 2.25 hrs, the mixture was heated to 50 $^{\circ}\mathrm{C}$. After 0.75 (m, 11H), 1.85 (d, 6.3 Hz, 1H), 2.27 (m, 1H), 2.76 (s, 2H), 5.42 (s, 1H), 6.07 (s, 1H), 6.99 (d, J = 7.5 Hz), 6H), 3.15 (t, 2H), 4.17 (d, J = 6.6 Hz, 1H), 4.48 (s, hrs, 3-chloromethylbenzoyl azide (0.025g, 0.128 mmol) foamy solid (0.309g, 62%). ¹H NMR (CDCl3) § 0.71 (t, 7.86 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 8.17 (s, 1H). J = 5.4 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H), 1.03-1.60 3-Chloromethylbenzoyl azide (0.142g, 0.726 mmol) bottom flask. The reaction flask was purged with N_2 , equipped with magnetic stirrer, and heated to 110 °C. After 2 hrs, the reaction mixture was cooled to R.T, and toluene (2.0 mL) were combined in a 10 mL round-7.18-7.26 (m, 2H), 7.30-7.41 (m, 3H), 7.63 (s, 1H), Example 1398 (0.365g, 0.796 mmol) was added. After stOAc/hexane and concentrated in vacuo gave a white and the 3-aminobenzothiepene prepared in Step 5 of to R.T. and concentrated in vacuo. Purification by was added, and the reaction mixture was heated to HRMS (M + Li). Calculated for C34H44N3O4SClLi: 532.2901. Found: 632.2889.

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Example 1437

Preparation of:

ú (m, 1H), 2.74 (s, 6H), 3.11 (m, 8H), 3.37 (m, 6H), 4.12 (8, 1H), 4.39 (8, 2H), 5.31 (8, 1H), 6.11 (8, 1H), 6.52 with ethyl ether, and dried in vacuo to yield a white solid (0.250g, 80%). mp 246.0-248.0 $^{\circ}$ C; † H NMR (CD30D) white precipitate had had formed. Ethyl ether (6.0 mL) 5 0.88 (m, 6H), 1.03-1.55 (m, 10H), 1.76 (m, 1H), 2.11 round-bottom flask. The reaction flask was purged with 1,4-Diazabicyclo(2.2.2)octane (0.157g, 1.40 mmol) 7.23 (d, J = 6.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.47 (m, (dd, J = 8.7, 1.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 55.06; H, 7.64; N, 9.48; S, 4.34; Cl, 4.80. Found: , and equipped with magnetic stirrer. A solution of was added, and the precipitate was filtered, washed and acetonitrile (1.00 mL) were combined in a 10 mL the product of Example 1436 (0.262g, 0.418 mmol) in acetonitrile (2.70 mL) was added. After 2.5 hrs, a 2H), 7.58 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H). HRMS. 702,4064. Anal. Calculated for C40H56N5O4SCl: C, Calculated for C40H56N5O4SCl: 702.4053. Found: 64.90; H, 7.77; N, 9.42; S, 4.16; Cl, 4.89.

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Example 1435

Preparation of:

Me₂N

with ethyl ether (10.0 mL). The precipitate was 37 °C. A solution of the product of Example 1434 with N_1 , equipped with magnetic stirrer, and heated to 3.30-3.50 (m, 8H), 4.10 (s, 1H), 4.21 (t, J = 5.4 Hz, 2.76 (s, 6H), 3.10 (m, 2H), 3.17 (t, J = 7.2 Hz, 6H), 1.16 (t, J = 6.6 Hz, 2H), 1.78 (m, 1H), 2.12 (m, 3H), to give a white solid (0.185g, 62%). mp 218.0-225.0 °C method was repeated, followed by concentrated in vacuo filtered to yield a white solid. This trituration was dissolved in acetonitrile (2.0 mL) and precipitated to R.T. and concentrated in vacuo. The crude product added. After 24 hrs, the reaction mixture was cooled diazabicyclo(2.2.2)octane (0.0490g, 0.437 mmol) was added. After 2.5 hrs, 1,4-diazabicyclo(2.2.2)octane (0.250g, 0.432 mmol) in acetonitrile (2.50 mL) was mL round-bottom flask. The reaction flask was purged mmol) and acetonitrile (1.0 mL) were combined in a 10 2H), 5.31 (s, 1H), 6.10 (s, 1H), 6.55 (d, J = 7.2 Hz1H NMR (CD3OD) & 0.90 (m, 6H), 1.05-1.55 (m, 10H), (0.0200g, 0.178 mmol) was added. After 64 hrs, 1,4-1,4-Diazabicyclo(2.2.2)octane (0.0785g, 0.700

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1H), 7.25 (d, J = 6.9 Hz, 1H), 7.33-7.42 (m, 2H), 7.56 (e, 1H), 7.76 (d, J = 9.0 Hz, 1H). HRMS. Calc'd for C36H55N4O5SCl: 655.3893. Found: 655.3880.

5 Example 1436

Preparation of:

Step 1. Preparation of:

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3-Chloromethylbenzoyl chloride (2.25 mL/15.8 mmol) and acetone (8.0 mL) were combined in a 25 mL round-bottom flask. The reaction flask was cooled to 0°C, and an aqueous solution of sodium azide (1.56g in 5.50 mL/24.0 mmol) was added. After 1.5 hrs, the reaction mixture was poured into ice water (80.0 mL), extracted with ethyl ether (2x25 mL), dried (MgSQ₁), and concentrated in vacuo to give a colorless oil (2.660g, 86%). 1H NMR (CDCl₃) & 4.62 (s, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.55 (s, 1H).

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Step 1: Preparation of monomethyl PEG mesylate

intermediate

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of triethyl amine, and to the resulting solution at 0°C Step without further purification and characterization. chloride. The resulting solution was stirred overnight 100 mL of methylene chloride was added 2.2 g (22 mmol) To a solution of 20 g of monomethyl ether PEG in was added dropwise 2.5 g (22 mmol) of methanesulfonyl nydrochloride was filtered off to give the monomethyl PEG mesylate intermediate which was used in the next at ambient temperature, and the triethyl amine

Step 2: Preparation of polyethylene-linked

benzothiepene

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nesylate PEG intermediate (obtained from Step 1) in 5.5 obtained from Example 1402, Step 10) in 5.5 mL of DMF was stirred at ambient temperature under N, for 30 min. A mixture of 38 mg (1.52 mmol 95%) of NaH and 0.7 compound as an oil: 1H NMR (CDCl,) & 0.9 (q, 6h), 1.05and the residue was extracted with methylene chloride 1.65 (m, 11H), 2.2 (t, 1H), 2.8 (B, 6H), 3.0 (q, 2H), 3.4 (8, 4H), 3.5-3.85 (m, 95H), 4.1 (s, 1H), 4.15 (t, overnight under N, at 50 °C. DMF was removed in vacuo To the solution was added 0.55 g (0.51 mmol) of the 2H), 5.5 (B, 1H), 6.05 (B, 1H), 6.6 (d, 1H), 6.9 (d, 4gSO,, and the concentrated residue was purified by dimethylamino)tetrahydrobenzothiepine-1,1-dioxide nL of DMF, and the resulting solution was stirred and washed with brine. The extract was dried over column chromatography to give the desired title g (1.52 mmol) of 5-(4'-hydroxyphenyl)-7-

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Example 1434

Preparation of:

eluting with 20% EtOAc/hexane and concentrated in vacuo 0.87-0.93 (m, 6H), 1.05-1.70 (m, 11H), 2.14 (t, J = 6.3 IH), 4.33 (t, J = 6.0 Hz, ZH), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.7 Hz, 1H), 6.65 (s, magnetic stirrer, and cooled to 0 °C. A solution of 3mL) was added, and the mixture was washed with $H_{2}O$ (2x4 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.34-7.39 (m, 2H), 7.54 chloropropyl chloroformate (1.440g, 1.10 mmol, 12% in nL), dried (MgSO,), filtered and concentrated in vacuo. (0.35 mL, 0.875 mmol, 10% in H₂O) and toluene (0.50 mL) (d, J = 7.2 Hz, 1H), 7.89 (d, 8.7 Hz, 1H). HRMS (M + gave a white solid (0.269g, 56%). 1H NMR (CDCl3) & Hz, 2H), 2.15-2.25 (m, 1H), 2.81 (8, 6H), 3.07 (ABq, CH,Cl,/ THF) was added. After 3.5 hrs, toluene (3.0 2H), 3.64 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 7.5 Hz, The 3-aminobenzothiepene prepared in Step 5 of Example 1398 (0.380g, 0.828 mmol), sodium hydroxide Purification by flash chromatography on silica gel reaction flask was purged with N,, equipped with H), Calc'd for C30H44N2O5SCl: 579.2659. Found: were combined in a 10 mL round-bottom flask.

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disp) of NaH in 28 mL of DMF was added 2.0 g (4.35 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.95 (d, 2H) 3.5 (t, 2H), 3.9 (m, 4H), 4.1 (d, 1H), 4.2 (d, 2H), 1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), ether intermediate: 'H NMR (CDCl₃) & 0.90 (q, 6h), 1.05purified by column chromatography to give bromoethyl was dried over MgSO,, and the concentrated residue was with ethyl acetate and washed with brine. The extract DMF was removed in vacuo and the residue was extracted continued at ambient temperature under N, overnight. mmol) of bis(2-bromoethy1)ether, and stirring was mmol) of 5-(4'-hydroxyphenyl)-7-Step 1: Preparation of bromoethyl ether intermediate 7.4 (d, 2H), 7.9 (d, 1H). for 30 min. To the solution was added 13.2 g (54.38 resulting solution was stirred at ambient temperature (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the To a stirred solution of 0.192 g (4.785 mmol, 60%

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Step 2: Preparation of diester intermediate

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overnight. Solvent was removed in vacuo and the residue Step 1). The mixture was stirred under N_{3} at 80 $^{\circ}\text{C}$ g (4.68 mmol) of dibenzyl malonate (Aldrich), and the in 45 mL of THF and 15 mL of DMF at 0 °C was added 1.33 chromatography to give the diester intermediate: 'H NMR concentrated residue was purified by column brine. The extract was dried over MgSO,, and the was extracted with methylene chloride and washed with mmol) of bromoethyl ether intermediate (obtained from resulting solution was stirred at ambient temperature 3H), 2.8 (8, 6H), 3.0 (q, 2H), 3.6 (t, 2H), 3.7 (m, (CDCl) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2-2.3 (m, for 15 min, followed by the addition of 0.95 g (1.56 To a mixture of 94 mg (2.34 mmol, 60% disp) of NaH

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2H), 7.9 (d, 1H). 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3 (m, 10H), 7.4 (d, 3H), 4.1 (m, 3H), 5.1 (s, 4H), 5.42 (s, 1H), 5.9

Step 3: Preparation of diacid

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H, 7.56; N, 2.13; S, 4.92. 5.4 (s, 1H), 6.05 (s, 1H), 6.55 (d, 1H), 6.98 (d, 2H), 3.58 (s, 1H), 3.78 (t, 2H), 4.08 (d, 1H), 4.15 (t, 2H), 2.25 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.47 (q, 2H), off, and the filtrate was concentrated to give the hydrogen gas for 2 hours. The catalyst was filtered of 10% Pd/C in 25 mL of ethanol and 5 mL of THF was diester intermediate (obtained from Step 2) and 35 mg C, 62.54; H, 7.47; N, 2.21; S, 5.06. Found: C, 61.75; 632.2893. Found: 632.2882. Anal. Calc'd for C11H(1NO,S: 7.42 (d, 2H), 7.8 (d, 1H). HRMS. Calc'd for C₁₃H₄₇NO₉S: desired title compound as a solid: mp 119.5 °C; 'H NMR agitated at ambient temperature under 20 psi of (THF-d8) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.1 (q, 2H) A suspension of 0.761 g (0.935 mmol) of the

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yl]phenoxy]methyl]-w-methoxypoly(oxy-1,2-ethanediyl) tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-(4R-cis)-a-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-

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6H),3.05 (m, 2H), 3.10 (ABq, 2H), 3.22 (m, 2H), 4.05 (a, 1H), 5.30 (a, 2H), 5.50 (a, 1H), 5.97 (a, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for C₃₅H₄N₃O₆S: 623.3155. Found: 623.3188.

Example 1431

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(4R-cis) -N- (Carboxymethyl) -N- [[6-[[4-[3,3-dibutyl-7(dimethylamino) -2,3,4,5-tetrahydro-4-hydroxy-1,1dioxido-1-benzothiepin-5-yl]phenoxy]methyl] -2pyridinyl]methyl]glycine

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Step 1: Preparation of pyridinyl diester intermediate

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A mixture of diethyl. aminodiacetate (89, 68 mmol) and sodium carbonate (0.53g, 5.9 mmol) was treated with picolyl chloride intermediate (0.72g, 1.2 mmol, obtained from Example 1430, Step 1), and stirred at 160 °C for three hours. The reaction was cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts were dried over MgSO, filtered and concentrated in vacuo. The residue was purified by distillation in the Kugelrohr to give pyridinyl diester intermediate as a yellowish foamy solid (0.72g, 80%): 'H NMR (CDCl,) & 0.84-0.95 (m, 6H), 1.02-1.5 (m, 16H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABQ, 2H), 3.70 (s, 4H), 4.2-4.4 (m, 6H), 5.30 (s, 2H), 5.56 (s, 1H), 6.02 (s, 1H), 6.60

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(d, 1H), 7.10 (d, 2H),7.50 (m, 3H), 7.61 (d, 1H), 7.80 (t, 1H), 7.95 (d, 1H). HRMS. Calc'd for C₄₁H₅N₁O₄S: 752.3945. Found: 752.3948.

Step 2: Preparation of pyridinyl diacid

A mixture of pyridine-aminodiacetate intermediate (0.7g, 0.93 mmol, obtained from Step 1), and lithium hydroxide monohydrate (0.18 g, 4.5 mmol) in THF/ water (25.0 mL, 1:1) was stirred at 40 °C overnight (18 hours). The reaction mixture was diluted with ether and washed with 1% HCl, water (20 mL), and brine (30 mL). The organic layers were dried over MgSO, filtered and concentrated in vacuo to give the desired title compound as a white solid (0.44g, 90%): mp 153-155 °C; ¹H NMR (CDCl₃) & 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (8, 6H), 3.10 (ABq, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.84 (d, 2H), 7.85 (d, 1H), 7.84 (d, 2H), 7.85

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HRMS. Calc'd for C,H,N,O,S: 696.3319. Found:696.3331.

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Example 1432

(4S-cis).[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethyl]propanedioic acid

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C₁₄H₄₁N₅O₅S₂: C, 61.79; H, 7.32; N, 4.24; S, 9.70. Found: C, 61.38, H, 7.47; N, 4.22; S, 9.95.

Nampte 1430

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(4R-cis)-6-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinepropanoic acid

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Step 1: Preparation of picolinyl chloride intermediate

2.1 mmol, obtained from Example 1402, Step 10) in mL). The organic layers were dried over MgSO4, diluted with ether and washed with water and brine (30 magnetic stirrer. The reaction was heated to reflux 2,6-bischloromethylpyridine (1.2g, 10.8 mmol). The mmol), tetrabutylammonium iodide (0.1g, 0.2 mmol) and acetone (50 mL) was added anhydrous K,CO, (0.45g, 3.2 4.10 (d, 2H), 4.65 (s, 2H), 5.20 (s, 2H), 5.45 (s, 1H) 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, intermediate as an oil (0.70g, 55%): 'H NMR (CDCl) & EtOAc/Hexane gave 0.75 g (55%) of the picolyl chloride purification through silics gel, eluting with 25% filtered and concentrated in vacuo. Chromatographic for overnight. After 18 hours, the reaction was flask was equipped with nitrogen gas adapter and (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (19, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), To a solution of 5-(4'-hydroxyphenyl)-7-

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5.95 (s, 1H), 6.50 (d, 1H), 7.0 (d, 2H),7.35-7.50 (m, 4H), 7.70-7.85 (m, 2H).

Step 2: Preparation of pyridinyl malonate intermediate

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gave pyridinyl malonate intermediate as a white foamy 12H), 7.5 (t, 1H), 7.9 (d, 1H). (d, 1H), 4.16 (t, 1H), 5.02(8, 2H), 5.08 (8, 4H), 5.44 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.22 (d, 2H), 4.05 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, solid (1g, 71%): ^{1}H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), phase column eluting with 50% acetonitrile/water and concentrated. The residue was purified by C-18 reversed organic layers were dried over MgSO, filtered and washed with water (25 mL), and brine (50 mL). The and extracted with 5% HCl with methylene chloride and heated at 90°C for overnight. The reaction was cooled chloride intermediate (1g, 1.67 mmol) was added and a dry three-neck flask. The flask was equipped with mL) and sodium hydride (0.13g, 3.3 mmol) were placed in (8, 1H), 5.97 (8, 1H), 6.96-7.10 (m, 3H), 7.20-7.32 (m nitrogen gas adapter and magnetic stirrer. The picolyl Dibenzyl malonate (1.42g, 5.01 mmol) in DMF (20.0

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Step 3: Preparation of pyridinyl acid

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The pyridinyl malonate intermediate (0.6g, 0.7 mmol, obtained from Step 2), THF/water (25.0 mL, 1:1) and lithium hydroxide monohydrate (0.14 g, 3.4 mmol) were placed in a 100 mL round-bottom flask. The reaction was stirred at ambient temperature overnight. After 18 hours, the reaction was extracted with 1% HCl and ether and then washed with water (20 mL) and brine (30 mL). The organic layers were dried over MgSO,, filtered and concentrated in vacuo gave the desired title compound as a white solid (0.44g, 90%): mp 105-107 °C; ¹H NMR (CDCl,) & 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s,

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 $^{\circ}C_{f}$ 'H NMK (CDCl₁) § 0.86-0.96 (m, 6H), 1.02-1.52 (m, 10H), 1.58-1.70 (m, 1H), 2.16-2.29 (m, 1H), 2.81 (g, 6H), 3.07 (AB_q, J_{Ag} = 15.3, 49.6 Hz, 2H), 4.10 (d, J = 7.5 Hz, 1H), 5.15 (g, 2H), 5.50 (g, 1H), 5.94 (d, J = 2.7 Hz, 1H), 6.51 (dd, J = 2.4, 8.7 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 7.39 (d, 6.0 Hz, 2H), 7.44 (g, J = 8.7 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 8.63 (dd, J = 1.6, 4.8 Hz, 2H).

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Step 2: Preparation of quaternary salt

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2.4 Hz, 1H), 6.61 (dd, J = 2.5, 8.7 Hz, 1H), 7.02 (d, J reversed phase chromatography (Waters-Delta prep) using 3.7 Hz, 1H), 8.14 (d, J = 6.3 Hz, 2H), 8.80 (d, J = 6.6 50-55% water/acetonitrile afforded 0.304 g (60%) of the 1.46 (8, 3H), 5.37 (8, 2H), 5.50 (8, 1H), 6.07 (d, J = desired title compound as a colorless solid: mp 96-99 Found: picolinyl intermediate (obtained from Step 1) in 10 mL 6H), 3.09 (AB_q, J_{AB} = 15.0, 27.9 Hz, 2H), 4.11 (8, 1H), = 8.7 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.90 (d, J = concentrated under a nitrogen stream. Purification by of acetonitrile and 3 mL of dichloromethane was added 137 mg (0.97 mmol) of iodomethane. The reaction was 10H), 1.57-1.70 (m, 1H), 2.12-2.27 (m, 1H), 2.84 (s, °C; ¹H NMR (CDC1,) 8 0.85-0.95 (m, 6H), 1.03-1.52 (m, To a stirred solution of 0.41 g (0.74 mmol) of stirred at ambient temperature for 16 hours, then Hz, 2H). HRMS Calc'd for C, H4, N,O,S: 565.3100.

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Example 1429

(4R-c1s)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium,
methanesulfonate (salt)

to give 6.14 g (79%). The filtrate was concentrated in 24.0 Hz, 2H), 3.88 (s, 1H), 4.40 (s, 3H), 5.21 (s, 3H), 2H), 7.64 (d, J = 8.7 Hz, 1H), 8.0 (d, J = 6.6 Hz, 2H), acetonitrile to give 1.09 g (14%). A total of 7.23 g (93%) of the desired title compound was obtained as an acetate. The solid was collected by vacuum filtration picolyl intermediate (obtained from Example 1428, Step 1) in 140 mL of acetonitrile heated at 70 °C was added 1H), 2.56 (s, 3H), 2.63 (8, 6H), 2.91 (ABq, J = 16.5, 1.56 g (14.6 mmol) methanesulfonic acid methyl ester. 9H), 1.42- 1.54 (m, 1H), 1.95-2.22 (m, 1H), 2.50 (8, 5.78 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 2.5, 8.7 Hz, 9.02 (d, J= 6.6 Hz, 2H). HRMS Calc'd for C,,H.,N,O,S: IH), 6.84 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.4 Hz, reaction was cooled and diluted with 50 mL of ethyl 0.66-0.76 (m, 6H), 0.85-0.95 (m, 1H), 0.95-1.35 (m, off-white solid: mp 232-233.5 °C; ¹H NMR (CDCl,) δ To a stirred solution of 6.5 g (11.8 mmol) of Heating was continued at 70 °C for 15 hours. The 565.3100. Found: 656.3087. Anal. Calc'd for vacuo and the residue crystallized from hot

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(d, 1H), 4.6 (8, 2H), 5.1 (8,2H), 5.5 (8, 1H), 6.0 (8, 1H), 6.6 (d,1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.8 (d,1H).

Step 2: Preparation of amino diester

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A mixture of 1.03 g (1.72 mmol) of chlorobenzyl intermediate (obtained from Step 1), 1.63 g (8.6 mmol) of diethyl amino diacetate, and 0.72 g (8.6 mmol) of NaHCO, in 30 mL of DMF was stirred at 100 °C for 6 hours. DMF was removed in vacuo and the residue was extracted with ether and washed with brine. The extract was dried over MgSO, and the concentrated residue was purified by column chromatography to give amino diester intermediate: ¹H NMR (CDCl₃) & 0.90 (q, 6H), 1.05-1.65 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55 (s, 4H), 3.95 (s, 2H), 4.1-4.2 (m, 5H), 5.05 (s, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (s, 6H), 7.8 (d, 1H).

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Step 3: Preparation of amino diacid

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0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.22 (t, 1H), 2.8 (s, title compound as a solid: mp 175 °C; 1H NMR (THF-d8) MgSO, and concentrated in vacuo to give the desired aqueous layer was extracted twice with ether, and the of LiOH in 30 mL of THF and 30 mL of water was stirred 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62. Calc'd for C3,H50N2O4S: C, 65.68; H, 7.25; N, 4.03; S, Calc'd for C, H50N,O,S: 695.3366. Found: 695.3359. Anal. 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS. 1H), 5.1 (8, 2H), 5.4 (8, 1H), 6.05 (8, 1H), 6.5 (d, 6H), 3.0 (t, 2H), 3.5 (8, 4H), 3.9 (8, 2H), 4.1 (d, combined extracts were washed with brine, dried over was diluted with ether and washed with 1% HCl. The at 40 °C under N, for 4 hours. The reaction mixture ester (obtained from Step 2) and 0.232 g (5.52 mmol) A solution of 0.863 g (1.15 mmol) of dibenzyl

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Example 1428

(4R-cis)-4-[[4-[3,3-Dibuty1-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium salt with trifluoroscetic acid (1:1)

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10 Step 1: Preparation of picolyl intermediate

picolinyl intermediate as a colorless solid: mp 95-98 saturated NH,Cl, diluted with 600 mL ethyl acetate were washed with brine, dried over MgSO,, and filtered 5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride oil dispersion, 35 mmol) of sodium hydride and the 1402, Step 10) in 200 mL of DMF was added 1.4 g (60% ethyl acetate/hexanes afforded 11.05 g (77%) of the silica gel chromatography (Waters-prep 500) using 60% filtered and concentrated in vacuo. Purification by for 17 hours. The reaction was quenched with 25 mL of solution of 4-picolyl chloride in diethyl ether was extracted with diethyl ether. The ethereal extracts was treated with cold saturated 'NaHCO, solution and hydrobenzothiepine-1,1-dioxide (obtained from Example reaction stirred at ambient temperature for one hour. (4'-hydroxyphenyl)-7-(dimethylamino)tetrawashed with 4X250 mL water, brine, dried over MgSO., The reaction was cooled in an ice bath and the To a stirred solution of 12.0 g (26.1 mmol) of 5-The reaction was stirred at ambient temperature

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1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for $C_{io}H_{34}N_{j}O_{i}S$: 674.3992. Found: 674.4005.

Example 1426a

(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1benzothiepin-5-yljphenoxylmethyl]phenyl]methyl]-4-aza1-azonlabicyclo[2.2.2]octane chloride

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A solution of the chlorobenzyl intermediate (4.6 g, 7.7 mmol, obtained from Example 1425, Step 1) in acetonitrile (100 mL) at 25°C under N, was treated with diazabicyclo[2.2.2]-octane (DABCO, 0.95 g, 8.5 mmol, 1.1 eq.) and stirred at 35°C for 2 hours, during which time a white solid precipitated out. The white solid was collected, washed with CH,CN and recrystallized from CH,OH/Et,O to give the title compound (4.95 g, 91%) as a white solid: mp 223-230°C (decomposed); ¹H NMR (CDCl₃) & 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (8, 6H), 3.06 (ABq, J = 15.1 Hz, J = 43.3 Hz, 2H), 3.16 (8, 6H), 3.06 (8H), 3.76 (8, 6H), 5.96 (8, 1H), 5.99 (8, 2H), 5.14 (8, 2H), 5.14 (8, 2H),

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6.99 (d, J = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for C₄C₄H₅N₅O₅S: 674.3992. Found: 674.4005.

Example 1427

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4R-cis) -N-(Carboxymethyl)-N-[[4-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-

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yl]phenoxy]methyl]phenyl]methyl]glycine

Step 1: Preparation of chlorobenzyl intermediate

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To a stirred solution of 144 mg (3.59 mmol, 60% disp) of NaH in 29 mL of DMF was added 1.5 g (3.26 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 45 min. To the solution was added 7.13 g (40.75 mmol) of dichloro p-xylene, and the mixture was stirred overnight. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSo, and the concentrated residue was purified by column chromatography to give the chlorobenzyl intermediate: ¹H NMR (CDCl₁) & 0.90 (g, 6H), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.1

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Purification by flash chromatography (5.4 x 45 cm silica, 25-40% EtOAc/hexane) afforded the chlorobenzyl intermediate (4.7 g, 72%) as a white foam: 'H NWR (CDC1₁) & 0.89-0.94 (m, 6H), 1.12-1.48 (br m, 10H), 1.63 (m, 1H), 2.22 (m, 1H), 2.81 (s, 6H), 3.05 (ABg, J=15.1 Hz, J=50.0 Hz, 2H), 4.11 (d, J=8.1 Hz, 1H), 4.60 (s, 2H), 5.11 (s, 2H), 5.48 (s, 1H), 5.96 (d, J=2.4 Hz, 1H), 6.48 (dd, J=8.9, 2.6 Hz, 1H), 7.00 (d, J=8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, J=8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, J=8.9 Hz, 2H)

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Step 2: Preparation of quaternary salt

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Hz, 1H), 8.58 (br s, 1H), 9.69 (d, J = 5.8 Hz, 2H); 8.9 Hz, 2H), 7.93 (t, J = 6.8 Hz, 1H), 8.34 (t, J = 7.7■ 7.7 Hz, 4H), 7.73 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 2.4 Hz, 1H), 6.26 (s, 2H), 6.41 (dd, J = 8.9, 2.4 Hz, 4.09 (a, 1H), 5.00 (a, 2H), 5.38 (a, 1H), 5.91 (d, J = 2.71 (8, 6H), 3.02 (ABq, J = 15.1 Hz, J = 28.4 Hz, 2H), HRMS. Calc'd for C,,H,,N,O,S: 641.3413. Found: 641.3425. 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, J6H), 1.06-1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H), yellow solid: mp 154-156 °C; 'H NMR (CDCl) 8 0.83 (m; to give the desired title compound (1.08 g, 96%) as a and stirred at 35 °C for 36 hours. The pale amber mL) at 25 °C under N_2 was treated with pyridine (5 mL) g, 1.7 mmol, obtained from Step 1) in acetonitrile (5 solution was cooled to 25 °C and concentrated in vacuo A solution of the chlorobenzyl intermediate (1.0

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Example 1426

(4R-cis)-1-[[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2,2,2]octane_chloride

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washed with 1 L of acetonitrile to give 9.6 g (93%) the for an additional 2 h. The product was collected and precipitate was formed. The slurry was stirred at 35°C diazabicyclo[2.2.2]octane (DABCO) in 40 mL of period to a solution of 2.9 g (26.2 mmol) of 60 mL of acetonitrile was added dropwise over a 30 min similar to the one outlined in Example 1425, Step 1) in chlorobenzyl intermediate (obtained from a procedure (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.26 (m, (8, 2H), 5.14 (8, 2H), 5.48 (8, 1H), 5.96 (8, 1H), 6.49 (s, 6H), 3.76 (s, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09 (8, 6H), 3.06 (ABq, J = 15.1 Hz, J = 43.3 Hz, 2H), <math>3.161.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 223-230°C (decomposed); ^{1}H NMR (CDCl₁) δ 0.89 (m, 6H), title compound as a colorless crystalline solid: mp acetonitrile at 35°C; during the addition, a colorless Under N₂, a solution of 8.7 g (14.5 mmol) of the

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Step 1: Preparation of benzoate intermediate

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15.1 Hz, 1H), 3.92 (8, 3H), 4.09-4.15 (m, 1H), 5.17 (8, nmol) of 95% sodium hydride and stirred for 10 minutes. intermediate: $^{1}{
m H}$ NMR (CDC1,) δ 0.86-0.96 (m, 6H), 1.14-(d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.93 (d, thiepine-1,1-dioxide (obtained from Example 1402, Step extracted with ethyl acetate, washed with brine, dried 2H), 5.49 (s, 1H), 5.94 (d, J = 2.2 Hz, 1H), 6.50 (dd, 2.80 (s, 6H), 2.99 (d, J = 15.1 Hz, 1H), 3.15 (t, J = To the reaction mixture was added 525 mg (2.29 mmol) J = 8.9, 2.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.43 10) in 10 mL dimethylformamide was added 35 mg (1.39 1.47 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.23 (m, 1H), To a solution of 0.53 g (1.15 mmol) of 5-(4'-. evaporated to afford 0.51 g (73%) of the benzoate ethyl 4-(bromomethyl)benzoate and stirred for 16 over magnesium sulfate, filtered and the solvent hours. Water was added to the reaction mixture, hydroxyphenyl) -7-(dimethylamino)tetrahydrobenzo-T = 8.9 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H)

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Step 2: Preparation of acid

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A solution of 0.51 g·(0.84 mmol) of the benzoate intermediate (obtained from Step 1) and 325 mg (2.53 mmol) of KOS1(CH,), (Aldrich) in 16 mL THF was stirred for 3.5 hours. The THF was evaporated, water added, extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.30 g (60%) of the desired tile compound as a white solid: mp 156 - 159 °C; 'H NMR (CDC1,) & 0.89-0.94 (m, 6H), 1.24-1.43 (m, 10H), 1.62-1.66 (m, 1H), 2.20-2.24 (m, 1H), 2.94 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (d, J = 15.1 Hz, 1H), 4.14 (s, 1H), 5.20 (s, 2H), 5.50 (s, 1H), 6.16 (s, 1H), 6.71 (d, J = 9.1 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.57 (d,

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J = 8.3 Hz, 2H), 7.95 (d, J = 8.9 Hz, 1H), 8.13 (d, J 8.1 Hz, 2H). HRMS. Calc'd for C₃,H₄NO₅S: 594.2889. Found: 594.2913.

Example 1425

(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1benzothlepin-5-yl]phenoxy]methyl]phenyl]methyl]pyridinium chloride

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Step 1: Preparation of chlorobenzyl intermediate

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A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N, was treated with powdered K,CO, (2.3 g, 16.3 mmol, 1.5 eq.) and α,α' -dichloro-p-xylene (6.7 g, 38.1 mmol, 3.5 eq.) and the resulting solution was stirred at 65 °C for 48 hours. The reaction mixture was cooled to 25 °C and concentrated to 1/5 of original volume. The residue was dissolved in ECOAc (150 mL) and washed with water (2 x 150 mL). The aqueous layer was extracted with ECOAc (2 x 150 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 150 mL). The combined extracts were diseconcentrated in vacuo to provide a yellow oil.

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dimethyl sulfoxide (20 mL) was added sodium azide (47 mg, 0.723 mmol, 1.1 eq), and the resulting clear solution was stirred at 23 °C for 16h. The reaction solution was diluted with 100 mL ethyl acetate, then washed with water (2x 100 mL) and brine (1x 100 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give 390 mg (quantitative) of pentyl azide intermediate as a yellow oil: 'H NMR (CDCl₃) & 0.82-0.90 (m, 7H), 1.05-1.56 (m, 12H), 1.59-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.82 (s, 6H), 3.08 (q, 2H), 3.44 (t, J = 7.7 Hz, 2H), 3.99 (t, J = 7.7 Hz, 2H), 4.91 (br s, 1H), 5.47 (s, 1H), 6.13 (d, J = 7.58 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 7.14 (ABq, 4H), 7.91 (d, J = 7.8 Hz, 1H).

Step 2: Preparation of amino ester intermediate

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amino ester intermediate as a yellow oil: ¹H NMR and brine (1x 20 mL). The organic layer was dried g, 1.54 mmol, 2.25 eg) and bromo acetic acid benzyl celite and concentrated in vacuo to give a yellow oil. 1H), 2.75 (d, J = 7.83 Hz, 1H), 2.795 (s, 6H), 3.08 (q, 1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J= 8.3 Hz, ethyl acetate (20 mL) and washed with water (2x 20 mL) concentrated in vacuo, and the residue was dissolved in stirred at 23 °C for 48 hours. The reaction was ester (0.212 g, 0.925 mmol, 1.35 eq). The reaction was under an atmosphere of hydrogen gas (48 psi) for 4.5 palladium on carbon in ethanol (15 mL) was agitated 0.684 mmol, obtained from Step 1) and 100 mg of 2H), 3.68-3.85 (m, 2H), 3.87-4.04 (m, 2H), 4.09 (s, (CDCl₃) & 0.82-0.90 (m, 6H), 1.05-1.56 (m, 14H), 1.58-(MgSO,) and dried in vacuo to give 420 mg (89%) of the mL), followed by the addition of triethylamine (0.156 hours. The ethanolic suspension was filtered through The oil was immediately diluted with acetonitrile (15 A suspension of pentyl azide intermediate (390 mg,

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1H), 5.147 (s, 1H), 5.46 (s, 1H), 5.98 (d, J = 7.58, 1H), 6.50 (dd, 1H), 6.85-6.87 (m, 2H), 7.28-7.45 (m, 5H), 7.89 (d, J = 8.0 Hz, 1H). MS (ES) m/e 693.

5 Step 3: Preparation of acid

A suspension of benzyl ester intermediate (0.420g, 0.61 mmol, obtained from Step 2) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 16h. The suspension was filtered through celite, and concentrated in vacuo to give 0.330g of a yellow semisolid. The material was triturated with diethyl ether and the remaining semi-solid was dried in vacuo to give 0.19 g (52%) of the desired title compound as a yellow semi solid: ¹H NMR (CDCl₁) & 0.86 (br s, 7H), 1.0-1.72 (m, 18H), 1.79 (br s, 2H), 1.98 (s, 2H), 2.09-2.24 (m, 2H), 2.78 (s, 6H), 2.99 (q, 2H), 3.96 (bs, 2H), 4.08 (s, 1H), 5.46 (s, 1H), 5.97 (s, 1H), 6:40-6.49 (m, 1H), 7.14 (ABq, 4H), 7.85 (t, J = 7.93 Hz, 1H). MS (ES) m/e 603.

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Example 1424

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(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]benzoic acid

mmol) of sodium azide and a catalytic amount of sodium organic layer was washed with brine, dried over MgSO,, filtered, and concentrated in vacuo to afford 155 mg concentrated under a nitrogen stream and the residue azide intermediate as a colorless foam. Sample was (92% RPHPLC purity, about 76% yield) of the pentyl partitioned between ethyl acetate and water. lodide. The reaction was stirred at ambient temperature for 64 hours. The reaction was

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(t, J = 6.3 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 4.09 (s, used without further purification: mp 45-50 °C; 1H NMR 2.81 (8, 6H), 3.06 (ABq, JAs = 15.0, 48.0 Hz, 2H), 3.31 1H), 5.47 (s, 1H), 6.10 (d, J = 1.8 Hz, 1H), 6.63 (dd, CDCl₃) & 0.83-0 93 (m, 6H), 1.03-1.48 (m, 10H), 1.54-J = 2.7, 9.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.39 1.74 (m, 5H), 1.78-1.86 (m, 1H), 2.14-2.26 (m, 1H), (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H). MS FAB, M+H) m/e 571.

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Step 2: Preparation of pentyl amine intermediate

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IH), 5.49 (8, 1H), 6.00 (d, J = 1.5 Hz, 1H), 6.51 (d, Jthrough celite and concentrated in vacuo to give 0.62 g The sample was used intermediate (obtained from Step 1) in 75 mL of ethanol (CDCl,) & 0.86-0.96 (m, 6H), 1.06-1.75 (m, 15H), 1.79-= 9.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = To a solution of 0.67 g (1.17 mmol) of the azide temperature for 3.5 hours. The reaction was filtered 3.20 (m, 4H), 3.99 (t, J = 6.0 Hz, 2H), 4.04-4.14 (m, 1.93 (m, 4H), 2.15-2.28 (m, 1H), 2.82 (s, 6H), 2.96-8.1 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). MS (ES, M+H) was added 0.10 g of 10% palladium on carbon and the without further purification: mp 70-85 °C; 'H NWR mixture shaken under 49 psi of hydrogen at ambient (86% RPHPLC purity, ca. 84%) of pentyl amine intermediate as an off-white foam.

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Step 3: Preparation of quanidine

pentyl amino intermediate (obtained from Step 2) and 81 (0.551)To a stirred solution of 258 mg (0.474 mmol) of mmol) of diisopropylethylamine. The reaction was lydrochloride in 1.5 mL of DMF was added 71 mg mg (0.551 mmol) of 1H-pyrazole-1-carboxamidine stirred at ambient temperature for 16 hours.

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foamy solid: mp 67.0-72.5 °C; 1H NMR (CDC1,) 8 0.89-0.93 2.24 (m, 1H), 2.81 (s, 6H), 2.99-3.19 (m, 4H), 3.98 (br 8.1 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.89 (d, J =8.7 Purification by reversed phase chromatography (Waters-(m, 6H), 1.05-1.17 (m, 1H), 1.26-1.90 (m, 16H), 2.07-Hz, 1H), 6.51 (dd, J = 2.1, 8.0 Hz, 1H), 6.92 (d, J = Delta prep) using 60% water/acetonitrile afforded 120 8, 2H), 4.12 (8, 1H), 5.46 (8, 1H), 6.01 (d, J = 2.1 mg (43%) of the desired title compound as colorless Hz, 1H). HRMS. Calc'd for C₁₂H₅₀N₄O₄S:586.3552. Found (M+H): 587.3620.

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Example 1423

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(4R-cis) -N- [5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1benzothiepin-5-yl]phenoxy]pentyl]glycine

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Step 1: Preparation of pentyl azide intermediate

To a solution of pentyl bromide intermediate (400 mg, 0.657 mmol, obtained from Example 1420, Step 1) in

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(t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Esterification of chelidamic acid

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A solution of 10 g (54.6 mmol) of chelidamic acid, 23.0 g (120.12 mmol) of 1-(3-dimethyl amino propyl)-3 ethyl carbodiimide hydrochloride, 1.33 g (10.8 mmol) of 4-dimethyl amino pyridine, and 12.4 mL (120.12 mmol) of benzyl alcohol in 100 mL of DMF was stirred at ambient temperature overnight under N₁. DMF was removed in vacuo and the residue was extracted with methylene chloride, washed with 5% NaHCO₁, 5% acetic acid, H₂O, and brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give dibenzyl chelidamic ester: ¹H NMR (CDC1₁) & 5.4 (s, 4H), 7.4 (m, 12H).

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Step 3: Preparation of pyridinyl benzyl ester

intermediate

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7.78 (s, 2H), 7.9 (d, 1H). concentrated residue was purified by column intermediate: 'H NMR (CDCl₃) & 0.90 (q, 6H), 1.05-2.0 chromatography to give the pyridinyl dibenzyl ester with brine. The extract was dried over MgSO,, and the residue was extracted with ethyl acetate and washed overnight at 40 °C. DMF was removed in vacuo, and the added 1.0 g (1.643 mmol) of the pentyl bromide and 0.716g (1.972 mmol) of dibenzyl chelidamic ester (8, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3-7.5 (m, 12H) (t, 2H), 4.1 (8, 1H), 5.4 (8, 4H), 5.42 (8, 1H), 6.0 (m, 19H), 2.2 (t, 1H), 2.8 (8, 6H), 3.0 (q, 2H), 4.0 intermediate and the mixture was stirred under N_2 ambient temperature for 1 hour. To the solution was (obtained from Step 2) in 17.5 mL of DMF was stirred at A solution of 79 mg (1.972 mmol, 60% disp) of NaH

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Step 4: Preparation of pyridinyl diacid

A suspension of 0.8813 g (0.99 mmole) of dibenzyl ester (obtained from Step 3) and 40 mg of 10% Pd/C in 35 mL of ethanol and 5 mL of THP was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mmp 143 °C; 1H NMR (THF-d8) 0.95 (q, 6H), 1.05-1.65 (m, 15H), 1.9 (m, 4H), 2.22 (t, 1H), 2.8 (s, 6H); 3.0 (t, 2H), 4.1 (s, 3H), 4.3 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.78 (d, 1H), 7.82 (s, 2H). HRMS. Calc'd for C₁, H₆,N₁O₅S: 711.3315. Found: 711.3322. Anal. Calc'd for C₁, H₆,N₁O₅S: C, 64.20; H, 7.09; N, 3.94; S, 4.51. Found: C, 62.34; H, 6.97; N, 4.01; S, 4.48.

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Example 1422

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(4R-c1s) - [5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]guanidine

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Step 1: Preparation of pentyl azide intermediate

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To a stirred solution of 200 mg (0.328 mmol) of the pentyl bromide intermediate (obtained from Example 1420, Step 1) in 0.75 mL of DMSO was added 32 mg (0.493

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J=2.5, 8.4 Hz, 1H), 6.91 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.7 Hz, 1H).

Step 2: Preparation of pentyl nitrile intermediate

(9H), 1.58-1.92 (m, 7H), 2.16-2.28 (m, 1H), 2.41 (t, J 4z, 1H), 6.92 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, In 1 mL of DMSO was added 37 mg (0.745 mmol) of sodium the pentyl bromide intermediate (obtained from Step 1) . 6.9 Hz, 2H), 2.83 (8, 6H), 3.08 (ABq, 15.0, 47.5 Hz, IH), 6.07 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 2.4, 8.7 (H), 7.92 (d, J = 8.7 Hz, 1H). MS (ES, M+H) m/e 555. organic layer was washed with brine, dried over MgSO,, (H), 4.01 (t, J = 6.2 Hz, 2H), 4.1 (s, 1H), 5.49 (s, filtered, and concentrated in vacuo to afford 278 mg concentrated under a nitrogen stream and the residue To a stirred solution of 378 mg (0.621 mmol) of .0.86-0.96 (m, 6H), 1.02-1.21(m, 1H), 1.21-1.52 (m, intermediate as a colorless foam: 1H NMR (CDC1,) & (93% RPHPLC purity, ca. 75%) of the pentyl nitrile The reaction was stirred at ambient partitioned between ethyl acetate and water. temperature for 16 hours. The reaction was

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Step 3: Preparation of tetrazole

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A solution of 275 mg (0.5 mmol) of the nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene was stirred with heating at 80 °C for 60 hours. The reaction was concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 226 mg of the desired title compound (75%) as a colorless foam: mp 80-85 °C; ¹H NMR (CDCl,) & 0.83-0.95 (m, 6H), 1.30-1.52 (m, 10H), 1.52-1.73 (m, 3H), 1.79-1.99 (m, 4H), 2.14-2.26 (m, 1H), 2.91 (s, 6H), 3.02-3.22 (m, 4H), 3.92-4.06 (m, 2H), 4.16 (s, 1H), 5.47 (s, 1H),

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6.28 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 2.7, 8.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 8.7 Hz, 1H). HRMS Calc'd for C₃₃H₄₄N₅O₄S: 598.3427. Found: 598.3443.

Example 1421

(4R-cis) -4-[[5-[4-[3,3-Dibuty]-7-(dimethylamino) 2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1lbenzothiepin-5-yl]phenoxylpentyl]oxy]-2,6pyridinecarboxylic acid

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Step 1: Preparation of pentyl bromide intermediate

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To a solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was add 6.0g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: 'H NMR (CDC1,) 8 0.90 (g, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4

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solid was dissolved in acetonitrile and precipitated with N,, sealed, equipped with magnetic stirrer and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100g, 0.580 vacuo to give an off-white foamy solid (1.141g). The was cooled to ambient temperature and concentrated in heated to 50 °C. After 15 hours, the reaction mixture Fischer Porter bottle. The reaction vessel was purged mmol) in 5 mL of acetonitrile were placed in a 4 oz. mmol, obtained from Example 1418, Step 1) and The pentyl bromide intermediate (1.002g, 1.64

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12.3 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.35 (s, 4H), 4.08 (br s, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.51 12H), 3.52 (br s, 6H), 3.72 (br s, 4H), 3.97 (br s, 1.01-1.70 (m, 30H), 1.76-2.08 (m, 12H), 2.18 (t, J= (0.843g, quantitative): ^{1}H NMR (CDCl₃) δ 0.85 (m, 12H), (d, J = 9.0 Hz, 2H), 6.86 (d, J = 7.8 Hz, 4H), 7.38 (d

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desired dibromide salt as an off-white foamy solid sticky solid was concentrated in vacuo to give the trituration method was repeated, and the resulting 10

was decanted to yield a sticky off-white solid. This with ethyl ether. After cooling to 0 °C, the solvent

as a white foamy solid (0.676g, 86%): mp 178.0-182.0 with 70% H,O/CH,CN to give the desired title compound J = 7.8 Hz, 4H), 7.83 (d, J = 8.7 Hz, 2H). The 30H), 1.75-2.06 (m, 12H), 2.16 (t, J = 12.9 Hz, 2H), °C; 'H NMR (CDCl₁) & 0.80-0.90 (m, 12H), 1.01-1.70 (m, dichloride salt using Biorad AG 2X8 resin and eluting dibromide salt was converted to its corresponding

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7.84 (d, J = 8.7 Hz, 2 H). HRMS. Calc'd for $C_{1i}H_{1i}N_{1}O_{i}S$. 6.87 (d, J = 8.4 Hz, 4H), 7.38 (d, J = 8.1 Hz, 4H), 6.49 (d, J = 9.0 Hz, 1H), 6.50 (d, J = 9.0 Hz, 1H), s, 6H), 3.70 (br s, 4H), 3.96 (t, J = 5.4 Hz, 4H), 4.08 2.79 (8, 12H), 3.03 (ABq, 4H), 3.33 (8, 12H), 3.49 (br 614.4118. Found: 614.4148 (s, 2H), 5.42 (s, 2H), 5.986 (s, 1H), 5.993 (s, 1H),

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Example 1420

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yl)pentyl|oxy|phenyl|-1-benzothiepin-4-ol 1,1-dioxide tetrahydro-5-[4-[[5-(1H-tetrazol-5-(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-

Step 1: Preparation of pentyl bromide intermediate

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2.82 (s, 6H), 3.06 (AB_q, $J_{AB} = 15.2$, 45.3 Hz, 2H), 3.44 Hz, 2H), 1.94 (p, J = 7.0 Hz, 2H), 2.12-2.26 (m, 1H), foam: mp 65-70 °C; 'H NMR (CDCl₃) & 0.84-0.98 (M, 6H), 500) using 25% ethyl acetate/hexanes afforded 10.17 g oil dispersion) of sodium hydride in 150 mL of DMF was 1H), 5.47 (8, 1H), 6.15 (d, J = 2.7 Hz, 1H), 6.68 (dd 1.04-1.52 (m, 10H), 1.58-1.65 (m, 3H), 1.82 (p, J = 6.8 Purification by silica gel chromatography (Waters-Prep ethyl acetate, washed with water, brine, dried over ambient temperature for 1.5 hours and quenched with 50 dibromopropane was added. The reaction was stirred at bath (15 °C) and 4.48 g (195 mmol) of 1,5-After 30 minutes the reaction was cooled in a water MgSO, filtered and concentrated in vacuo. mL of saturated NH,Cl. The reaction was diluted with added 9.0g (19.5 mmol) of 5-(4'-hydroxyphenyl)-7-(t, J = 6.7 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 4.10 (8 (85%) of the pentyl bromide intermediate as a colorless (obtained from Example 1402, Step 10) in portions. (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide To a stirred suspension of 1.01 g (25.4 mmol, 60%

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Step 2: Preparation of mono-quaternary salt

2.18 (m, 1H), 2.20 (s, 6H), 2.67 (t, 2H), 2.74 (s, 6H), 3.75 (m, 4H), 3.90 (t, 2H), 4.01 (s, 1H), 5.37 (s, 1H), 2.98 (ABq, 2H), 3.30-3.42 (m, 1H), 3.38 (s, 6H), 3.60the reaction mixture was concentrated in vacuo to give with ethyl ether. The solvent was decanted to yield a twice, and the resulting sticky solid was concentrated tetramethylethylenediamine (1.0 mL/6.62 mmol) in 30 mL of acetonitrile was stirred at 40 $\,^{\circ}\mathrm{C}$ for 12 hours, and was dissolved in acetonitrile (1.5 mL) and triturated white foamy solid (0.951g, 94%): 1H NMR (CDC1,) & 0.81 (0.853g, 1.40 mmol, obtained from Step 1), N,N,N',N'-(t, 6H), 0.96-1.64 (m, 13H), 1.62-1.85 (m, 4H), 2.03an off-white foamy solid (1.052g). The crude product in vacuo to give the mono-quaternary salt as an offsticky solid. This trituration method was repeated 5.92 (8, 1H), 6.41 (dd, 1H), 6.81 (d, 2H), 7.32 (d, The mixture of pentyl bromide intermediate 2H), 7.77 (d, 1H).

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Step 3: Preparation of di-quaternary salt

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The mono-quaternary salt (0.933g, 1.29 mmol, obtained from Step 2), iodoethane (0.300 mL/3.75 mmol), and acetonitrile (30.0 mL) were combined in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N, sealed, equipped with magnetic stirrer, and heated to 50 °C. After 24 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give a yellow foamy solid (1.166g). The solid was dissolved in methylene chloride/acetonitrile and precipitated with ethyl ether. After cooling to 0 °C overnight, the resulting solid was filtered, washed with ethyl ether and concentrated in vacuo to yield the di-quaternary salt as an off-white solid (1.046g, 92%): 'H NMR (CD,OD) § 0.59 (t, 6H), 0.70-1.10 (m, 9H), 1.16

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(t, 3H), 1.22-1.80 (m, 9H), 2.42 (s, 6H), 2.78 (d, 2H), 2.98 (s, 6H), 3.02 (s, 6H), 3.22-3.37 (m, 4H), 3.63-3.78 (m, 4H), 3.80 (s, 4H), 4.93 (s, 1H), 5.71 (s, 1H), 6.22 (dd, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.40 (d,

Step 4: Preparation of quaternary di-chloride salt

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The iodobromosalt (obtained from Step 3) was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H₂O/acetonitrile to give the desired title compound as a white foamy solid (0.746g, 84%): mp 193.0-197.0 °C; ¹H NMR (CD₂OD) & 0.59 (t, J = 6.0 Hz, 6H), 0.70-1.12 (m, 9H), 1.16 (t, J = 6.6 Hz, 3H), 1.24-1.90 (m, 9H), 2.50 (s, 6H), 2.78 (s, 2H), 3.08 (s, 6H), 3.11 (s, 6H), 3.24-3.50 (m, 4H), 3.68 (s, 2H), 3.81 (s, 2H), 4.16 (s, 4H), 5.02 (s, 1H), 5.72 (s, 1H), 6.19 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for C, Hy,No,SCI: 708.4541. Found: 708.4599.

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ample 1419

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[4R-[4a,5a(4R*,5R*)]]-N,N'-bis[5-[4-[3,3-Dibutyl-7(dimethylamino)-2,3,4,5-tetrahydro-4-bydroxy-1,1dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N,N,N'tetramethyl-1,6-hexanediaminium dichloride

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(d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS (M+H)

m/e 743:

Example 1417

(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-5-[4-[[5-[[2-(1H-imidazol-4yl)ethyl]amino]pentyl]oxy]phenyl]-1-benzothiepin-4-ol
1,1-dioxide

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A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) and 3.4 g (30.6 mmol) of histamine was heated to 50 °C for 17 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO,. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with ether to afford 588 mg (60%) of the desired title compound as a semi-solid: 'H NWR (CDCl₃) & 0.9 (m, 6 H), 1-1.7 (m, 14 H), 1.9 (m, 3 H), 2.0 (m, 2 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (m, 3 H), 3.2 (m, 2 H), 4.0 (m, 2 H), 4.1 (m, 3 H), 5.5 (s, 1 H), 6.0 (s, 1 H), 6.5 (m, 1 H), 6.8 (s, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (m, 3 H), 7.9 (d, J = 8 Hz, 1 H). MS (M+H) m/e 639.

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Example 1418

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5 (4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)pentyl]-N'-ethyl-N,N,N',N'-tetramethyl-1,2-ethanediaminium dichloride

30 25 20 15 10 0.84-0.95 (m, 6H), 1.02-1.56 (m, 10H), 1.58-1.70 (m, as a white foamy solid (1.7839, 80%): H NMR (CDCl) & mixture was extracted with EtOAc (3x50 mL). Organic mixture was stirred for 18 hours. The reaction was dibromopentane (6.0 mL/44.0 mmol), and the resulting DMF was stirred in a dry 100 mL round-bottom flask Step 1: Preparation of pentyl bromide intermediate 1H), 2.80 (s, 6H), 3.05 (ABQ, 2H), 3.42 (t, 2H), 3.98 3H), 1.78-2.03 (m, 4H), 2.15-2.24 (m, 1H), 2.77 (s, evaporation in vacuo gave pentyl bromide intermediate through silica gel eluting with 20% EtOAc/hexane and concentrated in vacuo. Purification by filtration layers were combined, dried (MgSO,), filtered and diluted with brine (100 mL) and H,O (20 mL), and the under N_3 . To this solution was added 1,5-10) and sodium hydride (0.250g, 6.25 mmol) in 30 mL of (t, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 5.99 (d, 1H), 6.50 (1.680g, 3.66 mmol, obtained from Example 1402, Step (dd, 1H), 6.91 (d, 2H), 7.40 (d, 2H), 7.88 (d, 1H). (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide A mixture of 5-(4'-hydroxyphenyl)-7-

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Example 1415

(4R-cis) -N-(Carboxymethyl)-N-[5-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl)phenoxy]pentyl]glycine

Step 1: Preparation of diester intermediate

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A mixture of 8.6 g (14.1 mmol) of pentyl bromide intermediate (obtained from Example 1413, Step 1), 65 g (0.35 mol) of diethylaminodiacetate and 7.5 g (71 mmol) of anhydrous Na,CO, was stirred at 160 °C for 3 hours. The reaction mixture was diluted with water and extracted with methylene chloride. The volatiles was removed in vacuo to give 9.6g (95%) of the diester intermediate. 'H NMR spectrum was consistent with the structure; NS (M+H) m/e 717.

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Step 2: Preparation of diacid

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The mixture of the diester intermediate (obtained from Step 1) and 2.7g (64.3 mmol) of LiOH in THF (75 mL) and water (50 mL) was stirred at 40 °C for 18 hours. The reaction mixture was acidified with 1% HCl and extracted with dichloromethane. The residue was triturated with hexane, filtered to give 8.9g (93%) of the desired title compound as a solid: mp 148-162 °C; 'H NWR (CD,OD) & 0.92 (t, 6H), 1.1-1.9 (m, 31H), 2.15 (t, 1H),2.8(s, 6H), 3.15 (ABq, 2H), 3.75(m, 1H), 4.1 (m, 6H), 5.3(s, 1H), 6.1 (s, 1H), 6.6 (d, 1H), 7.0(d,

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2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M+H) m/e 661. Anal. Calc'd for [C₃H₃N₃O₄S + 1.5H₃O]: C,61.11; H,8.06; N.4.07; S,4.66. Found: C,61.00; H,7.72; N,3.89; S,4.47.

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Example 1416

(4R-cis)-5-[4-[[5-[bis[2(Diethylamino)ethyl]amino]pentyl]oxy]phenyl]-3,3dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1benzothiepin-4-ol 1,1-dioxide

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oil. ¹H NMR (CDCl₃) § 0.8 (m, 6 H), 1-1.6 (m, 28 H), 1.8 2.9 (d, J = 15 Hz, 1 H), 3.1 (d, J = 15 Hz, 1 H), 3.9 (m, 2 H), 4.0 (m, 1 H), 4.1 (8, 1 H), 5.4 (8, 1 H), 6.0 reverse phase chromatography. The fractions containing N, N, N', N' -tetraethyl diethylenetriamine was heated to residue was dried and concentrated in vacuo to afford 840 mg (74%) of the desired title compound as a thick A solution of 1 g of pentyl iodide intermediate 80 °C for 4 hours. The mixture was dissolved in ethyl washed with brine, dried over magnesium sulfate, and the product were concentrated in vacuo, dissolved in (m, 2 H), 2.1 (m, 1 H), 2.5 (m, 18 H), 2.7 (8, 6 H), (8, 1 H), 6.4 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 acetate and saturated NaHCO,. The organic layer was ethyl acetate and washed with saturated NaHCO,. The (1.53 mmol, obtained from Example 1414, Step 1) in concentrated in vacuo. The residue was purified by

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1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 12H), 7.85 (d, 1H).

Step 3: Preparation of diacid

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A suspension of 0.539 g (0.664 mmol) of the dibenzyl ester intermediate (obtained from Step 2) and 25 mg of 10% Pd/C in 30 mL of ethanol was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 118 °C; 'H NMTR (CDCl₃) & 0.9 (d, 6H), 1.05-2.2 (m, 20H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 1H), 3.95 (s, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.85 (d, 1H). 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.87 (d, 1H). Anal. Calc'd for C₁,H₁NO₂S: C, 64.63; H, 7.82; N, 2.22; S, 5.08. Found: C, 63.82; H, 7.89; N, 2.14; S, 4.93.

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Example 1414

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Mey N S Bu

(4R-c1s)-3,3-Dibutyl-5-(4-[[5-(diethylemino)pentyl]oxy]phenyl]-7-(dimethylemino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

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Step 1: Preparation of pentyl iodide intermediate
To a solution of 5-(4'-hydroxyphenyl)-7(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (3
g, 6.53 mmol, obtained from Example 1402, Step 10) in

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5 5 ഗ 7.9 (d, J = 7 Hz, 1 H). H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), H), 4.1 (s, 1 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 3.2 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 4.0 (m, 14 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (d, J = 15 Hz, 1 8 0.9 (m, 6 H), 1-1.5 (m, 11 H), 1.6 (m, 3 H), 1.8 (m, mmol) of the pentyl iodide intermediate: 1H NMR (CDCl₃) with hexane/ethyl acetate (1/5) to afford 2.92g (4.46 residue was chromatographed over silica gel, eluting magnesium sulfate and concentrated in vacuo. The organic layer was washed with brine, dried over layer was extracted with ethyl acetate and the combined was diluted in ethyl acetate and water. The aqueous 15 minutes at room temperature and diiodopentane was mmol) of 95% sodium hydride. The mixture was stirred 100 mL of dimethylformamide was added 198 mg (7.83 added. After one hour at room temperature the mixture

Step 2: Preparation of amine

25 20 35 30 solid: 1H NMR (CDCl₃) & 0.89 (m, 6H), 1.20-1:47 (m, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.4 Hz, 6.00 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.2 Hz, 2.6 Hz, 6.3 Hz, 2H), 4.10 (d, J = 7.8 Hz, 1H), .5.48 (s, 1H), 1H), 2.74-2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, J=12H), 1.53-1.67 (m, 4H), 1.76-1.90 (m, 8H), 2.21 (m, magnesium sulfate and concentrated to yield 390 mg solution twice. The ethyl acetate layer was dried over The foam was dissolved in 10 mL of ethyl acetate and stirred at 100 °C overnight. The mixture was iodide intermediate (obtained from Step 1) and 279 mg washed with 50 mL of saturated sodium carbonate concentrated in vacuo to yield a yellowish brown foam (3.81 mmol) of diethylamine in 3 mL of acetonitrile was 2H), 7.90 (d, J = 9.0 Hz, 1H). (85%) of the desired title compound as a yellow foamy A solution of 550 mg (0.76 mmol) of the pentyl

1H), 5.42 (s, 1H), 6.1 (d, 1H), 6.6 (d, 1H), 6.9 (d 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of quaternary salt

The concentrated residue was purified by reverse phase chromatography to give the desired title compound as a 2.25 (m, 18H), 2.8 (s, 9H), 3.0 (q, 2H), 3.95 (t, 2H), 1.1 (8, 1H), 5.28 (t, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.4 (d, 2H), 7.82 (d, 1H), the solution was heated at 45 °C under N, for 10 days. C18 column chromatography. The obtained material was solid: mp 136 °C; ¹H NMR (CDCl,) & 0.95(q, 6H), 1.05-Found: 657.3736. Anal. Calc'd for Cooks,NyO,S.CH,O,S: C, intermediate (obtained from Step 1) was added 3.94 g .9 (t, 1H), 8.2 (t, 2H), 8.3 (q, 2H), 8.98 (d, 1H), 55.40; H, 7.50; N, 3.72; S, 8.52. Found: C, 62.9; H, 10.2 (d, 1H). HRMS. Calc'd for C,0H3,N2O,S: 657.3726. (30.5 mmol) of quinoline and 30 mL of acetonitrile. To 1.0g (1.53 mmol) of the pentyl mesylate exchanged to its mesylate anion by ion exchange 7:42; N, 3.56; S, 8.41.

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Example 1413

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(48-c18) - [5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenoxy]pentyl]propanedioic acid

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Step 1: Preparation of pentyl bromide intermediate

at ambient temperature for 1 hour. To the solution was 1402, Step 10), and the resulting solution was stirred nydrobenzothiepine-1,1-dioxide (obtained from Example added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and To a stirred solution of 0.63 g (15.72 mmol, 60% mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetradisp) of NaH in 85 mL of DMF was added 6.0 g (13.1 the mixture was stirred overnight at ambient

was extracted with ethyl acetate and washed with brine The extract was dried over MgSO,, and the concentrated the pentyl bromide intermediate: 1H NMR (CDC1,) 8 0.90 temperature. DMF was removed in vacuo and the residue residue was purified by column chromatography to give (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (8, 1H), 5.42 (8, 1H), 6.0 (8, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

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Step 2: Preparation of dibenzyl ester intermediate

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0.84 g (2.952 mmol) of dibenzyl malonate (Aldrich), and thromatography to give the dibenzyl ester intermediate: (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 1H), 3.9 (t, To the mixture of 59 mg (1.476 mmol, 60% disp) of 2H), 4.1 (d, 1H), 5.18 (s, 4H), 5.42 (s, 1H), 5.95 (s, NaH in 27 mL of THF and 9 mL of DMF at 0 °C was added 'H NMR (CDC1,) 8 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 washed with brine. The extract was dried over MgSO, and the concentrated residue was purified by column intermediate, and the mixture was stirred at 80 °C temperature for 15 min. To the solution was added residue was extracted with methylene chloride and overnight. Solvent was removed in vacuo, and the the resulting solution was stirred at ambient 0.5987 g (0.984 mmol) of the pentyl bromide

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and ethyl acetate to afford 500 mg (43%) of product as a semi-solid. H NMR (CDCl) & 0.8 (m, 6 H), 1-1.6 (m, 24 H), 2.1 (m, 1 H), 2.6 (s, 3 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.0 (d, J = 15 Hz, 1 H), 3.3 (m, 8 H), 4.0 (m, 4 H), 5.3 (s, 1 H), 5.9 (s, 1 H), 6.4 (m, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS m/e 615.

Example 1411

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(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-3-hydroxypyridinium, methanesulfonate (salt)

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A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 234 mg (2.46 mmol) of 3-hydroxy pyridine in 1 mL of dimethylformamide was heated at 70 °C for 20 hours. The solvent was evaporated and the residue was triturated with ether and ethyl acetate to afford 990 mg (86%) of product as a semi-solid: ¹H NMR (CDCl₁) & 0.9 (m, 6 H), 1-1.5 (m, 10 H), 1.7 (m, 1 H), 1.9 (m, 2 H), 2-2.4 (m, 3 H), 2.9 (s, 6 H), 3.1 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 4.1 (m, 3 H), 4.7 (m, 2 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J

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9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.7 (m, 1 H), 8.0 (m, 2 H), 8.2 (m, 1 H), 9.1 (s, 1 H). MS m/e 609

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5 Example 1412

(4R-cis)-1-[5-[4-[3,3-Dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-4-hydroxy-1,1-dloxido-1benzothiepin-5-yl]phenoxy]pentyl]quinolinium,
methanesulfonate (salt)

Step 1: Preparation of pentyl mesylate intermediate

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To a stirred solution of 231 mg (5.79 mmol, 60% disp.) of NaH in 22 mL of DMF was added 2.05g (4.45 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-hydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the mixture was added 18.02 g (55.63 mmol) of 1,5-diiodopentane and the solution was stirred overnight at ambient temperature. DMF was removed by high vacuum and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO, and the concentrated residue was purified by column chromatography to give the pentyl mesylate intermediate: 'H NMR (CDCl₃) & 0.90(q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6h), 3.0 (q, 2H), 3.22 (t, 2H), 3.95 (t, 2H), 4.1 (s,

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Step 1: Preparation of propyl tosylate intermediate

(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 filtrate was concentrated and the residue was dissolved (s, 3H), 2.80 (s, 6H), 3.03 (ABq, J = 15.1 Hz, J = 46.3 Hz, 2H), 3.93 (m, 2H), 4.06-4.13 (m, 4H), 5.44 (s, 1H), J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.38 (d, J = outanediol di-p-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting solution was stirred at 65 °C for 21 orange oil. Purification by flash chromatography (4.4 5.96 (s, 1H), 6.46 (dd, J = 8.9, 1.4 Hz, 1H), 6.85 (d, g, 10.9 mmol, obtained from Example 1402, Step 10) in nours. The cream-colored slurry was cooled to 25 °C 10H), 1.61 (m, 1H), 1.84 (m, 4H), 2.19 (m, 1H), 2.43 in EtOAc (150 mL). The organic layer was washed with propyl tosylate intermediate (6.0 g, 80%) as a white Foam: ^{1}H NMR (CDCl,) § 0.89 (m, 6H), 1.10-1.44 (br m, acetone (100 mL) at 25 °C under N, was treated with (MgSO,) and concentrated in vacuo to provide a pale 8.1 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.83 (m, 1H). powdered K,CO, (3.8 g, 27.2 mmol, 2.5 eq.) and 1,4and filtered through a sintered glass funnel. The saturated aqueous NaHCO, (2 x 150 mL) and saturated iqueous NaCl (2 x 150 mL). The extract was dried k 35 cm silica, 20-30% EtOAc/hexane) afforded the A solution of 5-(4'-hydroxyphenyl)-7-

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Step 2: Preparation of quaternary salt

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A solution of propyl tosylate intermediate (5.8 g, 8.5 mmol, obtained from Step 1) in acetonitrile (100 mL) at 25 °C under N, was treated with diazabicyclo[2.2.2] octane (DABCO, 1.1 g, 10.1 mmol, 1.2 eq.) and stirred at 45 °C for 6 hours. The pale yellow solution was cooled to 25 °C and concentrated in vacuo to provide an off-white solid. The residue was dissolved in a minimal amount of CH₂Cl, (5 mL) and diluted with Et₂O (100 mL) while vigorously stirring

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C4,H43N,O,S2: C, 64.71; H, 7.96; N, 5.27. Found: C, 64.36; C, H, N, O, S: 626.3992. Found: 626.3994. Anal. Calc'd for iz, J = 30.0 Hz, 2H), 3.05 (br s, 6H), 3.37 (br s, 6H) 223-231 °C (decomposed); ¹H NMR (CDC1,) § 0.86 (m, 6H), ..09-1.43 (br m, 12H), 1.61-1.90 (br m, 5H), 2.13 (m, 3.89 (m, 2H), 4.07 (d, J = 7.5 Hz, 1H), 5.39 (s, 2H), IH), 2.25 (8, 3H), 2.75 (8, 6H), 3.03 (ABq, J = 15.1 recrystallized from EtOAc/hexane to give the desired title compound (5.7 g, 85%) as colorless needles: mp 5.97 (d, J = 1.6 Hz, 1H), 6.44 (dd, J = 8.9, 2.0 Hz, IH), 6.87 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.1 Hz, precipitated. The white solid was collected and 2H), 7.80 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for for 3 hours, during which time a white solid H, 8.10; N, 5.32.

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Example 1410

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(4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]-N,N,N-triethyl-1-butanaminium

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A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 15 mL of triethylamine in 10 mL of acetonitrile was heated at 50 °C for 2 days. The solvent was evaporated and the residue was triturated with ether

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s benzothiepin-5-yl]phenoxy]butyl]-4-aza-1azoniabicyclo[2.2.2]octanemethanesulfonate (salt) 2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-

10 Step 1: Preparation of butyl mesylate intermediate

3.04 (8, 3H), 3.08 (ABq, 2H), 4.05 (t, J = 5.55 Hz, J = 9.0 Hz, 2.7 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.42 2H), 5.49 (8, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.52 (dd 2H), 4.11 (d, J = 6.90 Hz, 1H), 4.35 (t, J = 6.0 Hz, give 1.02 g (77%) of butyl mesylate intermediate as a gel column, and eluted with 30% ethyl acetate/hexane to (d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H).(m, 12H), 1.98 (m, 4H), 2.22 (m, 1H), 2.83 (s, 6H), white solid: 'H NMR (CDCl) 8 0.90 (m, 6H), 1.20-1.67 resulting white foam was chromatographed through silica off and the filtrate was concentrated in vacuo. The mmol) of potassium carbonate in 20 mL of acetone was mL of ethyl acetate. The insoluble solid was filtered concentrated in vacuo and the crude was dissolved in 30 stirred at reflux overnight. The mixture was thiepine-1,1-dioxide (obtained from Example 1402, Step 10), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88 hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-A mixture of 1.00 g (2.18 mmol) of 5-(4'-

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Step 2: Preparation of ester intermediate

15 10 Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H). 2.6 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.12.77 (8, 3H), 2.82 (8, 3H), 3.07 (ABq, 2H), 3.26 (t, J 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.9 Hz, mp 248-251 °C; H NMR (CDCl) 8 0.91 (m, 6H), 1.14-1.47 the desired title compound which was recrystallized concentrated in vacuo to yield a white foam. The foam - 7.1 Hz, 6H), 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (8, (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H), from methylene chloride and acetone as a white solid: filtered off and dried in vacuo to give 540 mg (88%) of was crushed and washed with ether. The solid was 80 °C for 4 hours. The reaction mixture was mmol) of DABCO in 10 mL of acetonitrile was stirred at intermediate (obtained from Step 1) and 191 mg (1.71 A solution of 520 mg (0.85 mmol) of butyl mesylate

Example 1409

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azoniabicyclo[2.2.2] octane-4-methylbensenesulfonate benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-

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Example 1407

azoniabicyclo[2.2.2]octane, 4-methylbenzenesulfonate 4R-cis) -1-[3-[4-[3,3-Dibuty1-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dloxido-1benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-(salt)

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Step 1: Preparation of propyl tosylate intermediate

(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (5.0 filtrate was concentrated and the residue was dissolved propanediol di-p-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and was filtered through a sintered glass funnel. The NMR (CDCl₁) § 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.63 g, 10.9 mmol, obtained from Example 1402, Step 10) in cosylate intermediate (6.0 g, 80%) as a white foam: "H and the resulting mixture was stirred at 65 °C for 21 The cream-colored slurry was cooled to 25 °C in EtOAc (150 mL). The organic layer was washed with aqueous NaCl (2 x 150 mL), and was dried (MgSO,) and acetone (100 mL) at 25 °C under N, was treated with powdered K,CO, (3.8 g, 27.2 mmol, 2.5 eq.) and 1,3saturated aqueous NaHCO, (2 x 150 mL) and saturated concentrated in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 \times 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl A solution of .5-(4'-hydroxyphenyl)-7-

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(m, 1H), 2.14 (m, 2H), 2.21 (m, 1H), 2.41 (s, 3H), 2.81 (8, 6H), 3.06 (ABq, J = 15.1 Hz, J = 49.0 Hz, 2H), 4.01 (t, J = 5.3 Hz, 2H), 4.10 (m, 1H), 4.26 (t, J = 5.9 Hz, (dd, J = 8.9, 1.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 2H), 5.29 (s, 1H), 5.48 (s, 1H), 5.98 (s, 1H), 6.51 7.30 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of quaternary salt

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°C for 14 hours. The pale amber solution was cooled to acetonitrile (15 mL) at 25 °C under N_3 was treated with 2.4 Hz, 1H), 6.49 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (d, J 3.3 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.9 2.18 (m, 1H), 2.22 (m, 2H), 2.27 (s, 3H), 2.78 (s, 6H), oil. The residue was dissolved in a minimal amount of 1.5 eq.) and stirred at 50 °C for 6 hours, then at 25 6H), 1.12-1.43 (br m, 9H), 1.61 (m, 1H), 1.65 (m, 1H), = 8.5 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.40 (d, J = compound (1.11 g, 90%) as a white amorphous solid: mp 3.07 (ABq, J = 15.1 Hz, J = 39.5 Hz, 2H), 3.49 (br s, diazabicyclo[2.2.2]octane (DABCO, 0.26 g, 2.34 mmol, vigorously stirring for 4 hours, during which time a 4.09 (d, J = 7:3 Hz, 1H), 5.46 (s, 1H), 5.96 (d, J = 6H), 3.68 (m, 1H), 3.74 (br s, 6H), 3.96 (br s, 2H), 1z, 1H); HRMS. Calc'd for C, H, M, O, S: 612.3835. Found: A solution of the propyl tosylate intermediate 35 °C and concentrated in vacuo to provide an amber 136.5-142 °C (decomposed); 'H NMR (CDCl,) 8 0.89 (m, CH₂Cl₃ (5 mL) and diluted with Et₃O (100 mL) while collected (Et,O wash) to give the desired title white solid precipitated. The white solid was (1.05 g, 1.56 mmol, obtained from Step 1) in

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Example 1406

2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1szoniabicyclo[2.2.2]octane, methanesulfonate (salt) benzothiepin-5-yllphenoxylpropyl]-4-aza-1-(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-

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Step 1: Preparation of dimesylate intermediate

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NMR (CDC1) δ 2.12 (quintet, J = 4.5 Hz, 4H), 3.58 (8) organic layer was washed with brine, dried over MgSO,, of methylene chloride was added 15.8 g (137.9 mmol) of 6H), 4.38 (t, J = 5.4 Hz) dimesylate intermediate as a clear yellowish oil: 'H and concentrated in vacuo to give 13.5 g (89%) of partitioned between ethyl acetate and IN HCl. The 30 minutes, then warmed to ambient temperature and methanesulfonyl chloride. The mixture was stirred for of 1,3-propanediol in 50 mL of triethylamine and 200 mL To a cooled (-20 °C) solution of 5.0 g (65.7 mmol)

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Step 2: Preparation of propyl mesylate intermediate

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10) and 6.0 g (26.1 mmol) of dimesylate intermediate othiepine-1,1-dioxide (obtained from Example 1402, Step hydroxyphenyl) -7-(dimethylamino)tetrahydrobenz-(obtained from Step 1) in 50 mL of acetone was added To a solution of 2.4 g (5.2 mmol) of 5-(4'-

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15 10 σı 6.65 (d, J = 8.7 Hz, 1H), 6.94(d, J = 8.6 Hz, 2H), 7.43 4.48 (t, J = 6.0 Hz, 2H), 5.49 (s, 1H), 6.11 (s, 1H), 2.14-2.32 (m, 3H), 2.84 (s, 6H), 3.02 (s, 3H), 3.08 0.95 (m, 6H), 1.06-1.52 (m, 10H), 1.57-1.70 (m, 1H), (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H). $(AB_q, J_{AB} = 15.0 \text{ Hz}, J = 46.9 \text{ Hz}, 4.09-4.18 (m, 3H),$ afforded 2.8 g (90%) of the propyl mesylate intermediate as a white foam: 'H NMR (CDCl) & 0.86washed with brine, dried over MgSO4, and concentrated between ethyl acetate and water. The organic layer was concentrated in vacuo. The residue was partitioned reflux overnight then cooled to ambient temperature and 3.6 g (26.1 mmol) of K,CO,. The reaction was heated to (Waters-Prep 500) using 36% ethyl acetate/hexanes in vacuo. Purification by silica gel chromatography

Step 3: Preparation of quaternary salt

30 25 20 8.9 Hz, 1H). MS (ES+) m/e 612.4. HRMS (ES+) Calc'd 6H), 3.73-3.83 (m, 2H), 4.06-4.17 9m, 3H), 5.47 (B, Hz, J = 42.2 Hz, 2H) 3.22-3.32 (m, 6H), 3.56-3.66 (m, for C₃₅H₅₄N₃O₄S': 612.3835. Found: 612.3840. = 8.6 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 1H), 5.97 (s, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.90 (d, J2H), 2.83 (s, 6H), 3.04 (s, 3H), 3.09 (ABq, J, = 15.6 1.57-1.70 (m, 1H), 2.12-2.25 (m, 3H), 2.28-2.39 (m, title compound as a white solid: mp. (dec) 230-235 °C; chloride/ethyl ether gave 1.3 g (91%) of the desired was stirred at 60 °C for three hours, then cooled to of acetonitrile was added 0.3g (2.9 mmol) of 1,4-Purification by trituration with methylene ambient temperature and concentrated in vacuo. diazabicyclo[2.2.2]octane (DABCO). The reaction mixture mesylate intermediate (obtained from Step 2) in 20 ml ¹H NMR (CDCl₃) 8 0.86-0.95 (m, 6H), 1.04-1.52 (m, 10H), To a solution of 1.2 g (2.0 mmol) of propyl

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(4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy-1-butanesulfonamide

Step 1: Preparation of sulfonic acid intermediate

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thiepine-1,1-dioxide (obtained from Example 1402, Step mixture was vigorously stirred for 4 h then allowed to ..5 equiv.) and 1,4-butane sultone (2.5 mL, 24.1 mmol, additional 16 h. The resultant white precipitate was provide 8.8 g (92%) of the desired sulfonic acid as a .5 equiv.) and stirred and heated at 65 °C for 64 h. with powdered potassium carbonate (3.3 g, 24.1 mmol, 10) in acetone (35 mL) at 25 °C under N, was treated iltered and washed with water and dried in vacuo to recrystallized from CH,CN/hexane to give the desired quenched by the addition of water (50 mL), until a solution cooled to 0 °C over a 30 min period. The colorless solution was added dropwise to a 4 N HCl sulfonic acid as colorless needles: mp 229-236 °C homogeneous mixture was obtained. The clear and hydroxyphenyl) -7-(dimethylamino)tetrahydrobenzowhite solid. A portion of the white solid was A solution of 7.4 g (16.1 mmol) of 5-(4'-The solution was allowed to cool to 25 °C and warm to ambient temperature and stirred for an

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decomposed); ¹H NMR (DMSO-d₆) § 0.82 (m, 6H), 1.02-

(decomposed,); h nak (Janso-d₄) o 0.62 (m, on), 1.02-1.33 (br m, 10H), 1.59 (m, 1H), 1.73 (m, 4H), 2.00 (s, 1H), 2.48 (m, 2H), 2.71 (s, 6H), 2.98 (s, 1H), 3.86

(s, 1H), 3.93 (m, 2H), 5.08 (s, 1H), 5.89 (s, 1H), 6.52 (dd, J=8.9, 2.4 Hz, 1H), 6.92 (d, J=8.3 Hz,

2H), 7.29 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.9 Hz, 1H); Anal. Calc'd for C₁₉H₄NO₃S₂: C, 60.48; H, 7.61; N, 2.35. Found: C, 60.53; H, 7.70; N, 2.42.

Step 2: Preparation of 7-(dimethylamino)benzothiepin-5-yl]phenoxy-1-butanesulfonamide

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To a solution of 1.12 g (1.88 mmol) of the sulfonic acid (obtained from Step 1) in 10 mL CH,Cl, was added 785 mg (3.77 mmol) PCl, and stirred for 1 hour. Water was added and the mixture was extracted

hour. Water was added and the mixture was extracted and and washed with brine. Dried with MgSO, filtered and solvent evaporated. To the residue was added 30 mL of 0.5M NH, in dioxane and stirred 16 hours. The precipitate was filtered and the solvent evaporated.

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The residue was purified by MPLC (33% EtcAc in hexane) to afford the desired title compound as a beige solid (125 mg, 11%): mp 108-110 °C; ¹H NMR (CDCl₃) & 0.85-0.93 (m, 6H), 1.13-1.59 (m, 10H), 1.60-1.67 (m, 1H), 1.94-

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2.20 (m, 5H), 2.82 (s, 6H), 2.99 (d, J = 15:3 Hz, 1H), 3.15 (t, J = 15.3 Hz, 1H), 3.23 (t, J = 7.7 Hz, 2H), 4.03 (t, J = 5.8 Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (s,

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4.03 (t, J = 5.8 Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (s, 2H), 5.47 (s, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 8.9, 2.6 Hz, 1H), 6.91 (d, J = 8.9 Hz, 2H), 7.41

(d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.9 Hz, 1H). HRMS. Calc'd for $C_{10}H_{4}N_{1}O_{4}S_{2}$: 595.2876. Found: 595.2874.

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Calc'd for: C10H41N4O3S C, 62.69; H, 7.37; N, 4.87 Calc'd for C,0H42N5O,S: 575.2712. Found: 575.2790. Anal. Found: C, 62.87; H, 7.56; N, 4.87.

Example 1404

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tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenoxy]pentanoic acid (4R-cis)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-

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Step 1: Preparation of ester intermediate

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9, 2.2 mmol, obtained from Example 1402, Step 10) in powdered KyCO, (0.45 g, 3.3 mmol, 1.5 eq.), benzyl 5acetone (10 mL) at 25 °C under N_2 was treated with (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.0 A solution of 5-(4'-hydroxyphenyl)-7-

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J = 7.9 Hz, 1H), 5.13 (s, 2H), 5.47 (s, 1H), 6.00 (d, J6H), 3.05 (ABq, J = 15.1 Hz, J = 47.7 Hz, 2H), 4.10 (d) 1H), 1.86 (m, 2H), 2.21 (m, 1H), 2.47 (m, 2H), 2.81 (a (CDCl₁) & 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.64 (m, intermediate (1.2 g, 86%) as a colorless oil: 1H NMR 30 cm silica, 20-40% EtOAc/hexane) afforded the ester residue. Purification by flash chromatography (2.4 x °C and was concentrated in vacuo to provide a yellow for 24 hours. The pale amber slurry was cooled to 25 mg), and the resulting solution was stirred at 65 °C catalytic amount of tetra-n-butylammonium iodide (2 bromovalerate (0.88 g, 3.3 mmol, 1.5 eq.) and a

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C₁₈H₅₁NO₆S: 650.3515. Found: 650.3473. 2H), 7.86 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for J = 8.7 Hz, 2H), 7.36 (m, 5H), 7.40 (d, J = 8.5 Hz, = 2.5 Hz, 1H), 6.50 (dd, J = 8.9, 2.5 Hz, 1H), 6.91 (d,

Step 2: Preparation of acid

7.84 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for $C_{11}H_{45}NO_6S$: = 8.7 Hz, 2H), 7.39 (m, 5H), 7.39 (d, J = 8.3 Hz, 2H), 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), 560.3046. Found: 560.3043. 4.00 (s, 2H), 4.09 (s, 1H), 5.45 (s, 1H), 5.99 (d, J= 2.81 (8, 6H), 3.05 (ABq, J = 15.1 Hz, J = 49.7 Hz, 2H), ¹H NMR (CDCl₃) & 0.90 (m, 6H), 1.10-1.46 (br m, 10H), compound (0.54 g, 63%) as a white foam: mp: 76-79 °C; silica, 1.5% EtOH/CH2Cl2) afforded the desired title Purification by flash chromatography (2.6 x 25 cm concentrated in vacuo to give a white foam. filtered through a plug of Celite (10 g) and the reaction mixture for 10 min. The mixture was an atmosphere of N_2 and nitrogen was bubbled through reaction time of 4 hours. The slurry was placed under bubbled through the slurry for 1 min, for a total wt \$) then stirred under an atmosphere (1 atm) of H_2 via hydrogen balloon. Every 10 min, hydrogen gas was °C was treated with 5% palladium on carbon (0.15 g, 10 mmol, obtained from Step 1) in ethanol (7.5 mL) at 25 A solution of the ester intermediate (0.99 g, 1.5

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Step 12: Preparation of acid

J = 9.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 1.65 (m, 1H), 2.17-2.21 (m, 1H), 2.85 (s, 6H), 3.02 (d, 1H), 4.72 (8, 2H), 5.51 (8, 1H), 6.17 (8, 1H), 6.74 (d, 8.5 Hz, 2H), 7.97 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for the solvent was evaporated to afford the desired title (CDC1,) & 0.89-0.94 (m, 6H), 1.19-1.43 (m, 10H), 1.61-J = 15.1 Hz, 1H), 3.17 (t, J = 14.9 Hz, 1H), 4.12 (8, The reaction mixture was filtered through celite and intermediate (obtained from Step 1) in 40 mL ethanol atmosphere of hydrogen gas (40 psi) for three hours. mp 119 - 123 °C; ¹H NMR with 10% palladium on carbon was placed under an A solution of 1.30 g (2.14 mmol) of ester C26H40NO6S: 518.2576. Found: 518.2599. compound as a white solid:

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(4R-cis) -N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenoxyacetyl]glycine

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Step 1: Preparation of glycine ester intermediate

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10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 thiepine-1,1-dioxide (obtained from Example 1402, Step To a solution of 6.4 g (13.9 mmol) of 5-(4'hydroxyphenyl) -7- (dimethylamino) tetrahydrobenzo-

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(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) to reflux for 2 days, cooled to ambient temperature and (90%) of glycine ester intermediate as a white foam: ¹H Purification by silica gel chromatography (Waters Prep-(d, J = 8.5 Hz, 2H), 7.17 (8, 1H), 7.47 (d, J = 8.3 Hz, The reaction was heated (8, 1H), 5.98 (s, 1H), 6.56 (d, J = 8.6 Hz, 1H), 6.98 acetate and water. The organic layer was washed with (m, 6H), 4.25 (q, J = 7.0 Hz, 2H), 4.57 (s, 2H), 5.50 stirred for 20 hours, then partitioned between ethyl 500) using 50% ethyl acetate/hexanes afforded 7.5 g 3.08 (ABq, JAs = 15.3 Hz, J = 48.9 Hz, 2H), 4.06-4.19 NMR (CDCl,) & 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (8, 6H), brine, dried over MgSO,, and concentrated in vacuo. ml of acetone was added 3.8 g (21.0 mmol) of Nof tetrabutylammonium lodide. (H), 7.91 (d, J = 8.7 Hz, 1H).

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Step 2: Preparation of acid

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11.6 Hz, 2H), 4.01 (8, 2H), 4.07 (8, 1H), 4.61 (8, 2H), Intermediate (obtained from Step 1) and 1.5 g LiOH.H,o A solution of 7.3 g (12.1 mmol) of glycine ester organic layer was washed with brine, dried over MgSO,, recrystallization from ethyl acetate gave 5.45 g (78%) 5H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 5.31 (8, 1H), 6.04 (8, 1H), 6.57 (d, J = 9.0 Hz, 1H), of the desired title compound as a white crystalline neated to 45 °C for 2 hours. This was then cooled to solid: mp 149-150 °C; $^{1}\mathrm{H}$ NMR (CD,OD) § 0.88-0.98 (m, m, 1H), 2.79 (8, 6H), 3.11 (ABq, J_{AB} = 15.3 Hz, J = 7.08 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), (36.3 mmol) in 60 mL of THF and 60 mL of water was partitioned between ethyl acetate and water. The 7.76 (d, J = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS (ES+) umbient temperature, acidified with 1 N HCl and and concentrated in vacuo. Purification by

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concentrated in vacuo. The residue was dissolved in 200 mL of water, brine, dried over MgSO, and chloride, and the combined extracts were washed with was separated and extracted with 300 mL of methylene solution to neutralize the mixture. The aqueous layer diluted with 300 mL of saturated sodium bicarbonate water. The mixture was warmed to 10 °C, and further ice bath at -10 °C, and slowly quenched with 300 mL of complete. The reaction was cooled in an acetone-dry (-5 °C to 0 °C) for 1 hour or until the reaction was 297 mmol), and the resulting solution was stirred cold chloride at -10 °C was added dropwise a solution of dioxide (obtained from Step 9) in 500 mL of methylene boron tribromide (297 mL, IM in methylene chloride, enriched (dimethylamino)tetrahydrobenzothiepine-1,1-To a solution of 47 g (99 mmol) of enantiomeric

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desired 5-(4'-hydroxyphenyl)-7from methylene chloride to give 37.5 g (82%) of the concentrated in vacuo to give the crude 4-hydroxyphenyl of water, 200 mL of brine, dried over MgSO, and temperature. The mixture was washed twice with 200 mL glacial acetic acid for 30 minutes at ambient 500 mL of ethyl acetate and stirred with 50 mL of intermediate. The solid residue was recrystallized

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Hz, 1H), 6.55 (dd, J = 9, 2.4 Hz, 1H), 6.88 (d, 8,7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 9 Hz, 2H) Hz, 1H), 4.11 (s, 2H), 5.48 (s, 1H), 6.02 (d, J = 2.4 (8, 6H), 3.00 (d, J = 15.3 Hz, 1H), 3.16 (d, J = 15.3(m, 10H), 1.57-1.72 (m, 1H), 2.14-2.28 (m, 1H), 2.83 white solid: 1H NMR .(CDCl₃) δ 0.84-0.97 (m, 6H), 1.1-1.5 (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide as a

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hydroxyphenyl)-7-Alternatively, enantiomeric-enriched 5-(4'-

intermediate just described, can be prepared via non-(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide, the

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5-(4'-hydroxyphenyl)-7conditions as in Step 7 and Step 9) to give the racemic through the synthetic sequences (under the same in Step 8, but with 2.2 equivalent of m-CPBA) gave the hydroxypropylsulfide (obtained from Step 4) with mracemic sulfone intermediate. The sulfone was carried chloroperbenzoic acid (under the similar conditions as chromatography separation. Oxidation of aryl-3enantioselective synthesis followed by chiral

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5 appropriate chiral chromatographic purification. desired enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-The two enantiomers were further separated into the (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (dimethylamino)tetrahydrobenzothiepine-1,1-dloxide by

Step 11: Preparation of ester intermediate

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7.37 (8, 5H), 7.42 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H). 0.88-0.94 (m, 6H), 1.13-1.46 (m, 10H), 1.60-1.64 (m, 1.30g (98%) of the ester intermediate: 'H NMR (CDCl) & (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H),Hz, 1H), 3.16 (t, J = 15.1 Hz, 1H), 4.11 (8, 1H), 5.26 dimethylformamide was added 60 mg (2.38 mmol) of 95% (s, 2H), 5.49 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.63 1H), 2.20-2.24 (m, 1H), 2.81 (s, 6H), 3.00 (d, J=15.1sulfate, filtered and the solvent evaporated to afford acetate, washed with brine, dried over magnesium added to the reaction mixture, extracted with ethyl reaction mixture was added 400 µL (2.52 mmol) of benzyl 2-bromoacetate and stirred for two hours. Water was sodium hydride and stirred for 15 minutes. To the thiepine-1,1-dioxide (obtained from Step 10) in 10 mL hydroxyphenyl) -7- (dimethylamino) tetrahydrobenzo-To a solution of 1.0 g (2.18 mmol) of 5-(4'-

1-oxide (4R,5R) was purified by silica gel chromatography (Waters Prep 500) using 15% ethyl acetate/hexane to give 13.44 g (77.7%) of the product as a white solid: ¹H NWR (CDC1,) & 0.87-0.97 (m, 6H), 1.16-1.32 (m, 4H), 1.34-1.48 (m, 4H), 1.50-1.69 (m, 4H), 1.86-1.96 (m, 1H), 2.88 (d, <u>J</u> = 13.0 Hz, 1H), 3.05 (d, <u>J</u> = 13.0 Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), 4.48 (s, 1H), 6.52 (dd, <u>J</u> = 9.9 Hz, 2.4 Hz, 1H), 6.94 (d, <u>J</u> = 9.4z, 2H), 7.13 (dt, <u>J</u> = 8.4 Hz, 2.4 Hz, 1H), 7.38 (d, <u>J</u> = 9.7 Hz, 2H), 7.82 (dd, <u>J</u> = 8.7 Hz, 1H), 7.38 tep 8. Preparation of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

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for 30 minutes. The solution was then neutralized with acid (37.28 mmol, Sigma) at 0 °C. After stirring at 0 saturated Na,SO, was added into the mixture and stirred chloride was added 9.46 g of 68% m-chloroperoxybenzoic dioxide (4R,5R) as a light yellow solid: 1H NMR (CDCl,) of for 2 hours, the mixture was allowed to warm up to enantiomerically-enriched tetrahydrobenzothiepine-1,1-8 0.89-0.95 (m, 6H), 1.09-1.42 (m, 12H), 2.16-2.26 (m, 1H), 3.14 (q, J = 15.6 Hz, 1H), 3.87 (8, 3H), 4.18 (s, 1H), 5.48 (s, 1H), 6.54 (dd, J = 10.2 Hz, 2.4 Hz, 1H), 6.96-7.07 (m, 3H), 7.40 (d, 3 = 8.1 Hz, 2H), 8.11 (dd, To a stirred solution of 13.44 g (31.07 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1concentrated in vacuo to give 13.00 g (97.5%) of the oxide (obtained from Step 7) in 150 mL of methylene room temperature and stirred for 4 hours. 50 mL of chloride layer was separated, dried over MgSO4, and 50 mL of saturated NaHCO, solution. The methylene J = 8.6 Hz, 5.9 Hz, 1H).

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Step 9. Preparation of enantiomerically-enriched 7-(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

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enantiomerically-enriched tetrahydrobenzothiepine-1,1-The mixture was sealed and stirred at 110°C overnight, Prep 500) using 20% ethyl acetate/hexane gave 12.43 g 100 mL of water, dried over MgSO, and concentrated in Reactor was added about 20 mL of neat dimethylamine. dissolved in 200 mL of ethyl acetate and washed with (4R,5R) as a colorless solid: 'H NMR (CDCl,) 8 0.87-0.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), vacuo. Purification on a silica gel column (Waters (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide dimethylamine was evaporated. The crude oil was dimethylamine (2.0 M in THF, 146 mmol) in a Parr and cooled to ambient temperature. The excess To a solution of 13.00 g (28.98 mmol) of dioxide (obtained from Step 8) in 73 mL of (90.5%) of the enantiomerically-enriched

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(4R,5R) as a colorless solid: 'H NWR (CDC1,) § 0.87-0.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), 2.81 (s, 6H), 2.99 (d, $\underline{\underline{U}}$ = 15.3 Hz, 1H), 3.15 (d, $\underline{\underline{U}}$ = 15.3 Hz, 1H), 3.84 (s, 3H), 4.11 (d, $\underline{\underline{U}}$ = 7.5 Hz, 1H), 5.99 (d, $\underline{\underline{U}}$ = 2.4 Hz, 1H), 6.51 (dd, $\underline{\underline{U}}$ = 8.7 Hz, 2.4 Hz, 1H), 6.94 (d, $\underline{\underline{U}}$ = 8.7 Hz, 2H), 7.90 (d, $\underline{\underline{U}}$ = 8.7 Hz, 1H). The product and determined to have real and representations of the product by the second of the second color and the second color

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8.7 Hz, 2.4 Hz, 1H), 6.94 (d, <u>J</u> = 8.7 Hz, 2H), 7.42 (d <u>J</u> = 8.4 Hz, 2H), 7.90 (d, <u>J</u> = 8.7 Hz, 1H). The product was determined to have 78% e.e. by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. Recrystallization of this solid from ethyl acetate/hexane gave 1.70 g of the racemic product. The remaining solution was concentrated and recrystallized to give 9.8 g of colorless solid. Enantiomeric excess of this solid was determined by chiral HPLC on a

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Chiralpak AD column using 5% ethanol/hexane as the eluent. It showed to have 96% e.e with the first eluting peak as the major product.

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Step 10: Demethylation of 5-(4'-methoxyphenyl)-7(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide
(4R,5R)

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vacuo. The crude aryl-3-hydroxypropylsulfide was purified by silica gel chromatography (Waters Prep 500) using 8% ethyl acetate/hexane to yield 33.00 g (72.5%) of the product as a light brown oil: 'H NMR (CDCl₁) & 0.90 (t, <u>J</u> = 7.1 Hz, 6H), 1.14-1.34 (m, 12H), 2.82 (s, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10 (s, 2H), 6.77-6.92 (m, 4H), 7.09 (d, <u>J</u> = 8.7 Hz, 2H), 7.41 (dd, <u>J</u> = 8.7 Hz, 5.7 Hz, 1H).

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Step 5. Preparation of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

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using 5% ethanol/hexane as the eluent. 7.23 (m, 1H), 7.99-8.04 (m, 1H). Enantiomeric excess $\underline{J} = 13.5 \text{ Hz}, 1\text{H}), 3.45 (d, \underline{J} = 12.3 \text{ Hz}, 1\text{H}), 3.69 (d, \underline{J})$ 78% e.e. with the first eluting peak as the major was determined by chiral HPLC on a (R,R)-Whelk-O column 1H), 6.83-6.93 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 7.18-= 12.3 Hz, 1H), 3.79 (a, 3H), 4.02 (q, \underline{J} = 15.6 Hz, as a colorless oil: ^{1}H NMR (CDCl₃) δ 0.82-0.98 (m, 6H), 1.16-1.32 (m, 12H), 2.29 (d, $\underline{J} = 13.8 \text{ Hz}$, 1H), 2.77 (d, enantiomerically-enriched aryl-3-hydroxypropylsulfoxide ethyl acetate/hexane to afford 19.00 g (95%) of the on a silica gel column (Waters Prep 500) using 15% was concentrated in vacuo. The crude oil was purified white solid was filtered off and the hexane solution and the crude solid was washed with 1 L of hexane. The 30°C freezer for 72 hours. The solvent was evaporated L of methylene chloride was added 31.50 g of 96% (1R)aryl-3-hydroxypropylsulfide (obtained from Step 4) in 1 oxaziridine diasolved the mixture was placed into a -(-)-(8,8-dichloro-10-camphor-sulfonyl)oxaziridine (100.34 mmol, Aldrich) at 2°C. After all the To a stirred solution of 20.00 g (47.78 mmol) of It showed to be

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Step 6. Preparation of enantiomerically-enriched aryl-3-propanalsulfoxide

Hz, 1H), 4,12 (d, $\underline{J} = 15.9 \text{ Hz}$, 1H), 6.84-6.89 (m, 3H), 1H), 8.02 (dd, \underline{J} = 8.7 Hz, 5.7 Hz, 1H), 9.49 (s, 1H). 7.03 (d, $\underline{J} = 8.4 \text{ Hz}$, 2H), 7.19 (dt, $\underline{J} = 8.4 \text{ Hz}$, 2.4 Hz (d, <u>J</u> = 13.8 Hz, 1H), 3.79 (s, 3H), 3.97 (d, <u>J</u> = 15.9 4H), 1.89-1.99 (m, 1H), 2.57 (d, J = 14.1 Hz, 1H), 2.91 1.11-1.17 (m, 4H), 1.21-1.39 (m, 4H), 1.59-1.76 (m, light orange oil: ^{1}H NMR (CDCl₃) δ 0.85-0.95 (m, 6H), enantiomerically-enriched aryl-3-propanalsulfoxide as a ethyl acetate/hexane to give 17.30 g (91%) of the oil was filtered through 500 mL of silica gel using 15% dried over MgSO,, and concentrated in vacuo. The crude acetate twice. The ethyl acetate layer was separated, was stirred at room temperature for 48 hours, 500 mL of mmol, Aldrich) at room temperature. After the mixture Step 5) and 20.96 g of sulfur trioxide-pyridine (131.16 enriched aryl-3-hydroxypropylsulfoxide (obtained from water was added to the mixture and stirred vigorously. were added 19.00 g (43.72 mmol) of enantiomerically-The mixture was then extracted with 500 mL of ethyl (131.16 mmol, Aldrich) in 200 mL dimethyl sulfoxide To a stirred solution of 13.27 g of triethylamine

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Step 7. Preparation of the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R, 5R)

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To a stirred solution of 17.30 g (39.99 mmol) of enantiomerically-enriched aryl-3-propanalsulfoxide (obtained from Step 6) in 300 mL of dry THF at -15°C was added 48 mL of 1.0 M potassium t-butoxide in THF (1.2 equivalents) under nitrogen. The solution was stirred at -15°C for 4 hours. The solution was then quenched with 100 mL of water and neutralized with 4 mL of concentrated HCl solution at 0°C. The THF layer was separated, dried over MgSO,, and concentrated in vacuo. The enantiomerically-enriched tetrahydrobenzothiepine-

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6.81-6.87 (m, 4H), 7.09 (d, J = 8.7 Hz, 2H), 7.27-7.33 27.00 g (75.5%) of the product as a brown oil: 'H NMR diethyl ether twice. The ether layers were combined, (CDCl,) & 3.24 (8, 1H), 3.80 (8, 3H), 3.99 (8, 2H), dried over MgSO, and stripped to dryness to afford (m, 1H).

Step 3. Preparation of dibutyl cyclic sulfate

Step 3a. Preparation of 2,2-dibuty1-1,3-propanediol.

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To a stirred solution of di-butyl-diethylmalonate sodium sulphate and concentrated in vacuo to give diol suspension was filtered. The filtrate was dried over 20°C and 40 ml of water, and 80 mL of 10% NaOH and 80 stirred at RT overnight. The reaction was cooled to 98.4 g (yield 95%) as an oil. MS spectra and proton acetone/dry ice bath was added LAH (1 M THF) 662 ml (Aldrich) (150g, 0.55 mol in dry THF (700ml) in an temperature between -20 to 0°C. The reaction was ml of water were added dropwise. The resulting and carbon NMR spectra were consistent with the (1.2 eq., 0.66 mol) dropwise maintaining the product.

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Step 3b. Preparation of dibutyl cyclic sulfite

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(221 g, 2.19 mol) in anhydrous methylene chloride (500 magnesium sulfate and concentrated under vacuum to give ml) was stirred at 0°C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise A solution of 2,2-dibutyl-1,3-propanediol (103 g, left. The mixture was washed with ice water twice then 0.548 mol, obtained from Step 3a) and triethylamine and within 5 min the solution turned yellow and then black when the addition was completed within half an hour. The reaction mixture was stirred for 3 hrs. at with brine twice. The organic phase was dried over 0°C. GC showed that there was no starting material

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128 g (100%) of the dibutyl cyclic sulfite as a black oil. Mass spectrum (MS) was consistent with the product.

Step 3c. Oxidation of dibutyl cyclic sulfite to

dibutyl cyclic sulfate

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To a solution of the dibutyl cyclic sulfite (127.5 under nitrogen was added ruthenium (III) chloride (1 g) acetonitrile and 500 ml of water cooled in an ice bath with brine. The organic phase was dried over magnesium concentrated under vacuum and to give 133 g (97.8%) of and sodium periodate (233 g, 1.08 mol). The reaction of ether and the ether extract was washed three times material left. The mixture was extracted with 300 ml sulfate and passed through celite. The filtrate was was stirred overnight and the color of the solution turned black. GC showed that there was no starting carbon NMR and MS were consistent with the product. the dibutyl cyclic sulfate as an oil. Proton and g, 0.54 mol, obtained from Step 3b) in 600 ml

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Step 4. Preparation of aryl-3-hydroxypropylsulfide

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idded 25 mL of concentrated sulfuric acid to make a 2.0 To a stirred solution of 27.00 g (108.73 mmol) of .35 g of 60% sodium hydride dispersion in mineral oil or 10 minutes. The mixture was allowed to warm up to (obtained from Step 2) in 270 mL of diglyme was added (obtained from Step 3c) was added at 0°C and stirred M solution that was refluxed overnight. The solution room temperature and stirred overnight. The solvent solution was washed with 200 mL of diethyl ether and 29.94 g (119.60 mmol) of the dibutyl cyclic sulfate (108.73 mmol) at 0°C. After gas evolution ceased, as evaporated and 200 mL of water was added. The solution was dried over MgSO, and concentrated in was extracted with ethyl acetate and the organic 1-fluoro-2-((4-methoxyphenyl)methyl)thiophenol

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benzothiepin-5-yllphenoxylpentyllthio]-1H-tetrazole-1-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-(4R-cis)-5-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-

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methoxyphenyl)methyl)-phenol Step 1. Preparation of 4-fluoro-2-((4-

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temperature and a solution of 139.71 g of 3evolution stopped. The mixture was cooled down to room mixture was stirred at 90°C for 1 hour until gas 100.0 g of 4-fluorophenol (0.89 mol) at 0°C. The hydride (0.94 mol) in 600 mL of dry toluene was added To a stirred solution of 23.66 g of 95% sodium

7.16 (m, 2H). solid: 1H NMR (CDCl₃) & 3.79 (s, 3H), 3.90 (s, 2H), 4.58 to yield 53.00 g (25.6%) of the product as a pink through a layer of 1 L of silica gel with neat hexane distillation. The crude dark red oil was filtered (8, 1H), 6.70-6.74 (m, 1H), 6.79-6.88 (m, 4H), 7.11-The remaining starting materials were removed by dried over MgSO,, and concentrated under high vacuum. mixture was cooled to room temperature and quenched with 500 mL of water. The organic layer was separated toluene was added. After refluxing for 24 hours, the methoxybenzyl chloride (0.89 mol) in 400 mL of dry

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Step 2. Preparation of 4-fluoro-2-((4-

methoxyphenyl)methyl)-thiophenol

Step 2a. Preparation of thiocarbamate

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mixture was allowed to warm to room temperature and 26.61 g of dimethylthiocarbamoyl chloride (215.30 mmol) 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol in 500 mL dispersion in mineral oil (279.90 mmol) at 2°C. The of dry DMF was added 11.20 g of 60% sodium hydride To a stirred solution of 50.00 g (215.30 mmol) of

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as a pale white solid: 'H NMR (CDCl₃) & 3.21 (s, 3H), stripped to dryness. The crude product was filtered acetate/hexane to yield 48.00 g (69.8%) of the product through a plug of 500 mL silica gel using 5% ethyl brine. The ether solution was dried over MgSO, and solution was washed with 500 mL of water and 500 mL of extracted with 500 mL of diethyl ether. The ether 100 mL of water in an ice bath. The solution was temperature overnight. The mixture was quenched with was added. The reaction mixture was stirred at room

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Step 2b. 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol Rearrangement and hydrolysis of thiocarbamate

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3.46 (B, 3H), 3.80 (B, 3H), 3.82 (B, 2H), 6.78-6.86 (M

3H), 6.90-7.00 (m, 2H), 7.09 (d, $\underline{J} = 8.7 \text{ Hz}$, 2H).

25 20 6.0 Hz, 8.7 Hz, 1H). 2.7 Hz, 1H), 7.08 (d, $\underline{J} = 8.7$ Hz, 2H), 7.49 (dd, $\underline{J} =$ 4.07 (8, 2H), 6.82-6.86 (m, 3H), 6.93 (dt, J = 8.4 Hz, washed with 5% ethyl acetate/hexane to give 46.00 g solution was cooled down to room temperature and diphenyl ether was refluxed at 270°C overnight. The $(CDCl_3)$ δ 3.02 (s, 3H), 3.10 (s, 3H), 3.80 (s, 3H), (95.8%) of the product as a pale yellow solid: 1H NMR to remove phenyl ether. The rearrangement product was filtered through 1 L of silica gel with 2 L of hexane thiocarbamate (obtained from Step 2a) in 200 mL of A stirred solution of 48.00 g (150.29 mmol) of

aqueous mixture was acidified to pH 6 with concentrated diethyl ether twice and placed in an ice bath. The 200 mL of THF was added 17.28 g of NaOH (432.06 mmol). HCl solution. The solution was extracted with 300 mL of added. The aqueous solution was washed with 200 mL of solvents were evaporated off and 200 mL of water was The mixture was refluxed under nitrogen overnight. The rearrangement product (above) in 200 mL of methanol and To a solution of 46.00 g (144.02 mmol) of the

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Step 10

hydochloride (fw 172.10g/mole) Aldrich DB, 720-1 (2.4 In a 250 ml single neck round bottom flask with millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N KOH (agueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium stir bar place 2- diethylamineoethyl chloride carbonate.

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was diluted with ether and extracted with 1 portion of ayer was dried over Magnesium sulfate and isolated by mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool In a separate 2-necked 250 ml round bottom flask to ice temperature. Next add phenol product (previous 5% NaOH, followed by water and then brine. The ether solution prepared above. Heat to 40C for 3 days. The with stir bar add sodium hydride (60% dispersion in product which contained no starting material by TLC removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (silica 99% ethyl acetate/1% NH4OH at 5ml/min.). step) 1.1 g (2.4 mmol in 5 ml DMF and the ether Isolated yield: 0.78 g (mass spec , and H1 NMR)

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Step 11

The product from step 10 (0.57gms, 1.02 millimole The solution was evaporated to dryness and redissolved Fischer-Porter bottle and heated to 45 C for 3 days. in 5 mls of chloroform. Next ether was added to the precipitate 0.7272 gms. Mass spec M-I = 587.9, $^{\rm A}{\rm H}$ chloroform solution and the resulting mixture was Ew 558.83 g/mole) and iodoethane (1.6 gms (10.02 mmilimoles) was place in 5 ml acetonitrile in a chilled. The desired product is isolated as a

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Example 1402

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Step 8

and concentrated in vacuo to give a white solid saturated aqueous NaCl, dried over MgSO4, filtered ether. The ether solution was washed with H2O, CO2/acetone bath and added to the reaction vessel. (28.5g/96% yield). 1H NMR confirmed the desired mixture was allowed to cool and was dissolved in ethyl and was heated to 60 C. After 20 h, the reaction The mixture was allowed to warm to room temperature C. Dimethylamine (17.1g/379mmol) was condensed via a was added, and the vessel was sealed and cooled to -78 and magnetic stirrer. The system was purged with $\mathrm{N}_2.$ The corresponding fluoro-compound (28.1g/62.6mmol) A Fisher porter bottle was fitted with N_2 line

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Step 9 C26H37O4NS fw=459.64 163 臣

v yield). IH NMR confirmed the desired structure. ether extracts were combined, washed with saturated extracted two times with ethyl ether. The CHCl3 and concentrated in vacuo to give the product (6.27g/98% aqueous NaCl, dried over MgSO₄, filtered, and quenched with 10% K_2CO_3 (100 mL). After 10 min, the 4 h, the reaction mixture was cooled to 0 C and was mixture was allowed to warm to room temperature After layers were separated, and the aqueous layer was boron tribromide (10.50g/41:9mmol) was added. The added. The reaction mixture was cooled to -78 C, and compound (6.62g/14.0mmol) and CHCl_3 (150 mL) were was purged with ${\bf N}_2$. The corresponding methoxywith ${\rm N}_2$ gas adaptor and magnetic stirrer. The system A 250-mL, 3-neck, round-bottom flask was equipped

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(140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2 . The filtrate was concentrated in vacuo to give a dark yellow-red oil (110.6g, 77% yield). ¹H NMR and MS [(M + H) ⁺ = 417] confirm the desired structure.

Step 6

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C25H33O4FS fw=448.59

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concentrated in vacuo to give the product (93.2g, 78% allowed to warm to room temperature After 3.5 h, the portionwise. After 30 min, the reaction mixture was equipped with $N_{\mathbf{2}}$ gas adaptor and mechanical stirrer. chloroperbenzoic acid (158.21g/531.7mmol) was added which was extracted with ethyl ether. The organic layers were combined, dried $({\rm MgSO}_4)$, filtered, and sulfide (110.6g/265.5mmol) and $\mathrm{CH}_2\mathrm{Cl}_2$ (1.0 L) were An emulsion formed The system was purged with N_2 . The corresponding through a fine fritted funnel. The filtrate was reaction mixture was cooled to 0 C and filtered added. The solution was cooled to 0 C, and 3-A 2-liter, 4-neck, round-bottom flask was yield). ¹H NMR confirmed the desired structure. washed with 10% agueous K2CO3.

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Step 7

C25H33O4FS fw=448.59

added via addition funnel. After 1h, 10% ag/ HCl (1.0 equipped with ${\rm N}_2$ gas adaptor, mechanical stirrer, and three times with ethyl ether, dried (MgSO $_4$), filtered, a powder addition funnel. The system was purged with THF (1.0 L) were added, and the mixture was cooled to from 95/5 toluene/ethyl acetate to give a white solid 0 C. Potassium tert-butoxide (23.35g/208.1mmol) was (33.60g, combined yield: 71%). 1H NMR confirmed the N_2 . The corresponding aldehyde (93.2g/208mmol) and L) was added. After 1 h, the mixture was extracted acetate to give a white solid (32.18g). The mother liquor was concentrated in vacuo and recrystallized purified by recrystallized from 80/20 hexane/ethyl and concentrated in vacuo. The crude product was A 2-liter, 4-neck, round-bottom flask was desired product.

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C14H13OFS fw=248.32

98% yield). 1H NMR confirmed desired structure concentrated in vacuo to give an amber oil (463.0g, ether extracts were dried (MgSO,), filtered, and with conc. HCl, and extracted with ethyl ether. The dissolved in ethyl ether (1.0 L), and extracted with temperature, the mixture was concentrated by rotavap and the solution was stirred for 15 h. Potassium was heated to reflux for 4 h. After cooling to room hydroxide (425.9g/7.590mol) was added, and the mixture temperature, MeOH (2.0 L) and THF (2.0 L) were added, then heated to reflux for 2 h. After cooling to room mixture was stirred for 64 h. at room temperature and and the solution was heated to reflux for 2 h. The 2-(3-methoxybenzyl)-phenyldimethylthiocarbamate condenser. The system was purged with N_2 . 4-Fluoro- N_2 gas adaptor, mechanical stirrer, and reflux (605.3g/1.895mol) and phenyl ether (2.0kg) were added The aqueous extracts were combined, acidified A 12-liter, round-bottom flask was equipped with

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Step 4

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C25H35O2FS fw=418.61

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equipped with N_2 gas adaptor and mechanical stirrer. A 5-liter, 3-neck, round-bottom flask was

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G confirm the desired structure. concentrated in vacuo to give an amber oil ether solution was dried $(MgSO_4)$, filtered, and (143.949/85% yield). ¹H NMR and MS $((M + H)^{+} = 419)$ temperature, and extracted with ethyl ether. The heated to reflux for 30 min, cooled to room conc. ${\rm H}_2{\rm SO}_4$ was added. The aqueous solution was aqueous solution was washed with ethyl ether, and concentrated by rotavap and dissolved in H20. The stirred for 64 h. The reaction mixture was was added slowly, and the mixture was allowed to warm was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) methoxyethyl ether (1.0 L) were added and the solution methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-(110.89g/443.6mmol) was added, and the mixture was to room temperature 2,2-Dibutylpropylene sulfate The system was purged with N_2 . 4-Fluoro-2-(3-

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Step 5

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C25H33O2FS fw=416.59

added and cooled to 0 C. Pyridinium chlorochromate alcohol (143.94 g/343.8 mmol) and $\mathrm{CH_2Cl_2}$ (1.0 L) were equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with ${
m N}_2$. The corresponding A 2-liter, 4-neck, round-bottom flask was

C17H18NO2FS fw=319.39

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The

dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added ether. The combined organic layers were washed with into $\mathrm{H}_2\mathrm{O}$ (4.0 L), and extracted two times with ethyl dimethylthiocarbamoyl chloride (242.4g/1.961mol) was product (605.3g, 97% yield). $^1\mathrm{H}$ NMR and MS [(M+H) $^+$ added. After 15 h, the reaction mixture was poured $\mathrm{H}_2\mathrm{O}$ and saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated in vacuo to give the methoxybenzyl)-phenol (455.5g/1.961mol) and slowly. After warming to room temperature, system was purged with N2. 4-Fluoro-2-(3-

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Step 3

320] confirm desired structure.

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Step 2

added via addition funnel over a period of 2.5 h. The

reaction mixture was heated to reflux (100 C) for 1h.

fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was

(126.0g/4.988mol) in toluene (2.5 L) was added, and

the mixture was cooled to 6 C. A solution of 4-

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with reflux condenser, N_2 gas adaptor, mechanical

stirrer, and an addition funnel. The system was

purged with N2. A slurry of sodium hydride

refluxing, the mixture was cooled to room temperature

and poured into $m H_2O$ (2.5 L). After 20 min. stirring,

addition funnel while maintaining reflux. After 15 h.

(783.0g/5.000mol) in toluene (750 mL) was added via

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A solution of 3-methoxybenzyl chloride

the layers were separated, and the organic layer was

(720g) in MeOH (2.5 L). The MeOH layer was added to extracted with a solution of potassium hydroxide

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10% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5

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The toluene washes were extracted with 20% ag. KOH. All 20% agueous KOH solutions were times with toluene.

ether, dried over ${\rm MgSO_4}$, filtered and concentrated in acidic solution was extracted three times with ethyl combined and acidified with concentrated HCl.

(449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ¹H vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil

NMR and MS [(M + H) + = 233] confirmed desired structure.

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Step 10

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over anhydrous potassium carbonate. minutes and then separate by ether extraction and dry 34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15 bar place 2- diethylamineoethyl chloride hydochloride In a 250 ml single neck round bottom Flask with stir (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 mmol,4.12g),

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product may be further purified by chromatography removing ether by rotary evaporation (1.3 gms). The NaOH, followed by water and then brine. The ether diluted with ether and extracted with 1 portion of 5% Isolated yield: 0.78 g (mass spec , and H1 NMR) layer was dried over magnesium sulfate and isolated by prepared above. Heat to 40C for 3 days. The product 1.1 g (2.4 mmoles in 5 ml DMF and the ether solution temperature. Next add phenol product (previous step) oil, 100 mg , 2.6 mmol) and 34 ml of DMF. Cool to ice (SiO2 99% ethyl acetate/1% NH4OH at 5ml/min.). which contained no starting material by TLC was stir bar add sodium hydride (60% dispersion in mineral In a separate 2-necked 250 ml round bottom flask with

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Step 11

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10 v gms. (Mass spec M-I = 587.9, H NMR). desired product is isolated as a precipitate 0.7272 solution and the resulting mixture was chilled. The chloroform. Next ether was added to the chloroform evaporated to dryness and redissolved in 5 mls of placed in 5 ml acetonitrile in a fischer-porter bottle 558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was The product from step 10 (0.57gms, 1.02 millimole fw and heated to 45 C for 3 days. The solution was

Example 1401

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Step 1

A 12-liter, 4-neck round-bottom flask was equipped

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was added. After 1 h, the mixture was extracted three concentrated in vacuo. The crude product was purified by recryst. from 80/20 hexane/ethyl acetate to give a Potassium tert-butoxide (23.35g/208.1mmol) was added times with ethyl ether, dried $(MgSO_4)$, filtered, and toluene/ethyl acetate to give a white solid (33.60g/ combined yield: 71%). 1H NMR confirmed the desired via addition funnel. After 1h, 10% ag/ HCl (1.0 L) concentrated in vacuo and recrystelized from 95/5 were added, and the mixture was cooled to 0 C. The mother liquor was white solid (32.18 g). product.

Step 8

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The mixture was allowed to cool and was dissolved in ethyl added, and the vessel was sealed and cooled to -78 C. The mixture was allowed to warm to room temperature A Fisher porter bottle was fitted with ${\rm N}_2$ line and corresponding fluoro-compound (28.1g/62.6mmol) was magnetic stirrer. The system was purged with N_2 . Dimethylamine (17.1g/379mmol) was condensed via a 302/acetone bath and added to the reaction vessel. and was heated to 60 C. After 20 h, the reaction ether. The ether solution was washed with ${\rm H}_2{\rm O},$

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concentrated in vacuo to give a white solid (28.5g/96% saturated aqueous NaCl, dried $(MgSO_4)$, filtered, and yield). $^1 ext{H}$ NMR confirmed the desired structure.

Step 9

C26H37O4NS fw=459.64

A 250-mL, 3-neck, round-bottom flask was equipped with $N_{\rm 2}$ gas adaptor and magnetic stirrer. The system was tribromide (10.50g/41.9mmol) was added. The mixture quenched with 10% ${\rm K_2CO_3}$ (100 mL). After 10 min, the extracted two times with ethyl ether. The ${
m CHCl}_3$ and concentrated in vacuo to give the product (6.27g/98% purged with ${\rm N}_2$. The corresponding methoxy-compound ether extracts were combined, washed with saturated was allowed to warm to room temperature After 4 h, layers were separated, and the aqueous layer was yield). ¹H NMR confirmed the desired structure. (6.62g/14.0mmol) and CHCl₃ (150 mL) were added. reaction mixture was cooled to -78 C, and boron the reaction mixture was cooled to 0 C and was aqueous NaCl, dried (MgSO $_4$), filtered, and

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NMR and MS $[(M + H)^{+} = 419]$ confirm the desired structure.

Step 5

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2 . The corresponding alcohol (143.94g/343.8mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2 . The filtrate was concentrated in vacuo to give a dark yellow-red oil (110.6g, 77% yield). 1H NMR and MS [(M + H) $^+$ = 417] confirm the desired structure.

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Step 6

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C₂₅H₃₃O₄FS fw=448.59

15 10 desired structure. the product (93.2g, 78% yield). ^{1}H NMR confirmed the ethyl ether. The organic layers were combined, dried $({\rm MgSO_4})$, filtered, and concentrated in vacuo to give K2CO3. An emulsion formed which was extracted with funnel. The filtrate was washed with 10% aqueous was cooled to 0 C and filtered through a fine fritted room temperature After 3.5 h, the reaction mixture 30 min, the reaction mixture was allowed to warm to acid (158.21g/531.7mmol) was added portionwise. After solution was cooled to 0 C, and 3-chloroperbenzoic system was purged with N_2 . The corresponding sulfide with N_2 gas adaptor and mechanical stirrer. The A 2-liter, 4-neck, round-bottom flask was equipped (110.6g/265.5mmol) and $\mathrm{CH_2Cl_2}$ (1.0 L) were added. The

Step 7

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2 . The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L)

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The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/l.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried (MgSO₄), filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ¹H NMR and MS ((M+H) $^+$ = 320) confirm desired structure.

Step 3

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Cl4H13OFS fw=248.32

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A 12-liter, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate

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methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temparature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temparature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with

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M₂O. The aqueous extracts were combined, acidified with concentrated HCl, and extracted with ethyl ether. The ether extracts were dried (MgSQ₄), filtered, and concentrated in vacuo to give an amber oil (463.0g, 98% yield). ¹H NMR confirmed desired structure.

Step 4

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C25H35O2FS fw=418.61

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ether solution was dried $(MgSO_4)$, filtered, and conc'd methoxyethyl ether (1.0 L) were added and the solution was added slowly, and the mixture was allowed to warm Sodium hydride (9.68g/383.2mmol) methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2concentrated ${\rm H_2SO_4}$ was added. The aqueous solution A 5-liter, 3-neck, round-bottom flask was equipped in vacuo to give an amber oil (143.94g/85% yield). to room temparature, 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was concentrated by rotavap and dissolved in H2O. The agueous solution was washed with ethyl ether, and temperature, and extracted with ethyl ether. The was heated to reflux for 30 min, cooled to room with N_2 gas adaptor and mechanical stirrer. stirred for 64 h. The reaction mixture was system was purged with N_2 . 4-Fluoro-2-(3was cooled to 0 C.

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concentrated in vacuo. Purification by at ambient temperature for 18 hours. The reaction was mmol) of pyridine in 30 mL of acetonitrile was stirred A solution of 1.09 g (2.0 mmol) of 9 and 4.9 g (62 1.19 g (96%) of 10 as an off white solid. MS (FAB') recrystallization from methanol/ diethyl ether gave

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Example 1400

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Step 1

purged with ${\bf N_2}$. A slurry of sodium hydride A 12-liter, 4-neck round-bottom flask was equipped fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was the mixture was cooled to 6 C. A solution of 4-(126.0g/4.988mol) in toluene (2.5 L) was added, and stirrer, and an addition funnel. The system was with reflux condenser, N_2 gas adaptor, mechanical reaction mixture was heated to reflux (100 C) for 1h. added via addition funnel over a period of 2.5 h. The

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A solution of 3-methoxybenzyl chloride

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refluxing, the mixture was cooled to room temperature addition funnel while maintaining reflux. After 15 h. and poured into H_2O (2.5 L). After 20 min. stirring, (783.0g/5.000mol) in toluene (750 mL) was added via

with 20% ag. KOH. All 20% ag. KOH solutions were ether, dried $(MgSO_q)$, filtered and concentrated in combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl times with toluene. The toluene washes were extracted stirred for 30 min. The mixture was then washed 5 20% aqueous potassium hydroxide, and the mixture was the layers were separated, and the organic layer was (720g) in MeOH (2.5 L). The MeOH layer was added to extracted with a solution of potassium hydroxide

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vacuo. The crude product was purified by Kugelrohr NMR and MS $[(M + H)^+ = 233]$ confirmed desired distillation to give a clear, colorless oil structure. (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. H

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Step 2

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C₁₇H₁₈NO₂FS fw=319.39

purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-phenol mechanical stirrer and N_2 gas adaptor. The system was A 12-liter, 3-neck round-bottom flask was fitted with (455.5g/1.961mol) and dimethylformamide were added.

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Step 7. Preparartion of 7

and heated to 110 °C for 16 hours. The reaction vessel added 100 mL of a 2.0 M solution of dimethyl amine and THF contained in a stainless steel reaction vessel was 2H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (8, IH), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 20 mL of neat dimethyl amine. The vessel was sealed To a solution of 24.5 g (52.9 mmol) of 6 in 20 mL of colorless oil. 1H NMR (CDCl,) d 0.85 (t, J = 7.25 Hz, 5H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 was cooled to ambient temperature and the contents acetate/hexanes gave 21.8 g (84 %) of 7 as a clear 1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 15 % ethyl .H), 9.36 (8, 1H).

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Step 8. Preparation of 8

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A solution of 21.8 g (44.8 mmol) of 7 in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium

t-butoxide was added slowly, maintaining the

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acetate/hexanes as the elutant to give 3.0 g of 8 as a acetate and water, dried over MgSO4 and concentrated in vacuo. Purification by recrystalization from -10% solid. The mother liquor was purified by silica gel quenched with 50 mL of saturated ammonium chloride. temperature at <5 °C. Stirred for 30 minutes, then ethyl acetate/hexanes gave 15.1 g of 8 as a white chromatography (Waters Prep-500) using 30% ethyl The organic layer was partitioned between ethyl white solid. MS (FABLi*) m/e 494.6. HRMS (EI*) calculated for M+H 487.2756. Found 487.2746.

Step 9. Preparation of 9

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IM solution of boron tribromide was added. Stirred at ethyl acetate/methylene chloride gave 1.95 g (89%) of methylene chloride was cooled to -60 °C. 4.1 mL of a chloride and water, dried over MgSO, and concentrated in vacuo. Purification by recrystalization from 50% 9 as a white solid. MS (FABH*) m/e 537. HRMS (FAB) reaction to ~10 °C and quenched with 50 mL of water. The organic layer was partitioned between methylene ambient temperature for thirty minutes. Cooled A solution of 2.0 g (4.1 mmol) of 8 in 20 mL of calculated for M 536.1834. Found 536.1822.

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Step 10. Preparation of 10

HO²HO

7.32 7.09 6.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (8, 2H), 4.42 (8, 2H), d 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), dried the organic layer over MgSO, and condensed in 1.46 (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), elutant gave 24.2 g (60%) of 4 as a oil. 'H NMR (CDCl₁) To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of vacuo. Purification by silica gel chromatography quenched with water and warmed to ambient temperature. (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, followed by the addition of 22.4 g triethyl silane trifluoromethane sulfonic acid (12.8 mL, 144 mmol) 3 in 200 mL of methylene chloride was added 21.6 g (Waters Prep-500) using 10% ethyl acetate/ hexanes as Partitioned between methylene chloride and water, â, (E) J = 7.45 Hz, 1H, 7.15 - 7.21 (m, 2H), 7.25 -2H), 7.42 (m, 1H).

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Step 5. Preparation of 5 20

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pyridine complex (195 mmol). Stirred at ambient of 4 in 100 mL DMSO was added 31.2 g sulfur trioxide temperature for thirty minutes. Poured into cold water To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) and extracted three times with ethyl acetate. Washed

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5.64 Hz, 1H), 9.40 (s, 1H). 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and J = 7.46 Hz, 1H, 7.14 (s, 1H), 7.19 (d, <math>J = 7.65 Hzand 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, 3H), 4.15 (8, 2H), 4.43 (8, 2H), 6.81 (dd, J = 9.66 Hz ¹H NMR (CDCl₃) d 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 vacuo to give 23.1 g (96 %) of 5 as a light brown oil. (300 mL), dired organics over MgSO, and condensed \underline{in} organics with 5% HCl (300 mL) and then with brine (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s,

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Step 6. Preparation of 6

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oil. H NMR (CDCl₃) d 0.86 - 1.29 (m, 14H), 1.58 - 1.63 chloride. Dried organic layer over MgSO, and condensed (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (8, 2H), 3.39 (8, mL 10% Na₂SO₃, partitioned between water and methylene ambient temperature for 24 hours. Quenched with 100 cholorperoxy-benzoic acid (112.6 mmol). Stirred at To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of 5 lH), 7.10 - 7.33 (m, SH), 8.05 (8, 1H), 9.38 (8, 1H) 3H), 4.44 (8, 2H), 4.50 (8, 2H), 6.93 (d, J = 9.07 Hz in vacuo to give 24.5 g (98%) of 6 as a light yellow in 200 mL methylene chloride was added 28.6 g meta

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vacuo. Purified by silica-gel chromatography through a minutes. Poured reaction contents into 1.0 L of water organic layer was dried over MgSO, and concentrated in 103.2 g (80%) of 1 as a clear colorless liquid. 'H NMR mmol) slowly via addition funnel. Then was added 182 200 mL plug using hexanes (100%) as elutant yielded funnel. Stirred at ambient temperature for fifteen (CDC1,) d 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, DMSO was added 120 g of 2-bromobenzyl alcohol (641 and extracted three times with ethyl acetate. The g of methyliodide (80 mL, 1282 mmol) via addition 2H), 7.12 (d, J = 7.45, 1H), 7.50 (s, 1H).

Step 2. Preparation of 2

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the organic layer was dried over MgSO, and concentrated (576 mmol). The mixture was stirred for one hour, and in 1.5 L THF was added 240 mL of 2.5 M n-butyl lithium thirty minutes, allowed to warm to 5 C, cooled to -10 To a cooled (-78 °C) solution of 95 g (472 mmol) of 1 'C and to it was added 6 g of Pd(PPh,), (5.2 mmol) and then to it was added 180 g of zinc iodide (566 mmol) in vacuo. Purification by silica.gel chromatography (Waters Prep-500) using 5% ethyl acetate/hexanes as 125 g 2,5-difluorobenzoyl chloride (708 mmol). The noursand then cooled to 10 °C, quenched with water, elutant gave 53.6 g (43 %) of 2 as an orange oil. dissolved in 500 ml THF. The mixture was stirred mixture was stirred at ambient temperature for 18 washed organic layer with 1N HCL and with 1N NaOH. partitioned between ethyl acetate and water, and

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NMR (CDC1,) d 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H).

Step 3. Preparation of 3

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7.25 Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 Added 1 L water to organic residue and extracted twice with diethyl ether. Aqueous layer acidified (pH 1) and extracted with methylene chloride, dried organic layer (242.8 mmol) in 250 mL DMF was heated to 100 °C for 18 2.82 Hz, 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, silica gel chromatography (Waters Prep-500) using 10% hours. The reaction was cooled (0 $^{\circ}$ C) and 60.7 g of X $^{'}$ ethyl acetate / hexanes as elutant gave 42.9 g (48 %) (the cyclic sulfate compound of example 1397) (242.8 A solution of 53 g (202.3 mmol) of 2 and 11.2 g Li2S refluxed 2 days. Cooled to ambient temperature and of 3 as a yellow oil. 'H NMR (CDCl,) d 0.86 (t, J = 8.26 Hz and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and (a, 2H), 3.40 (g, 3H), 4.48 (g, 3H), 7.02 (dd, J = over MgSO, and condensed in vacuo. Purification by mmol) in 50 mL DMF was added. Stirred at ambient temperature for 18 hours then condensed in vacuo. 2H), 7.69 (d, J = 7.85 Hz, 1H), 7.74 (8, 1H).

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Step 8

C12H4, NO, SI fw = 701.71

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Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 60% disp. in mineral oil) in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill NaH with ice bath and begin N_3 purge.

Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 mls anhydrous DMF. Add to the cold NaH. Stir at cold temperature for 30 min. Add 1.33 gms K₂CO₃ (9.57 mmoles Fisher P-208).

Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane (43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous DMF. Add to cold reaction mixture. Warm to room

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Cleanup by diluting with ether and extracting sequentially with 5% NaOH, H₂O, and saturated NaCl. Dry organic layer with MgSO₄, filter and dry. Obtain pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and mass spec (m/z=702).

temperature then heat to 40°C overnight under N2.

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H,C CH₁

C38H63N3O6SI fw=802.90

Dissolve 1.0 gms (1.43 mmoles) of product 8 with 10 mls anhydrous acetonitrile. Place in a 3 ounce Fischer-Porter pressure reaction vessel with magnetic stir bar. Add 2.9 gms triethyl amine (28.6 mmoles Aldrich 23,962-3) dissolved in 10 mls anhydrous acetonitrile. Purge well with N, then close system. Heat at 45°C. Monitor reaction by TLC. Reaction is usually complete in 48 hrs.

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Perform cleanup by removing acetonitrile under vacuum. Redissolve with anhydrous chloroform and precipitate quaternary ammonium salt with ether. Repeat several times. Dry to obtain crystalline product. Obtain NMR and mass spec (m/z=675).

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Example 1399

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Step 1. Preparation of 1

To a solution of 144 g of KOH (2560 mmol) in 1.1 L of

Step 6

Dissolve 8.97 gms (0.0189 mole) of product 5 with 135 mls anhydrous THF. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N, inlet and stopper. Chill solution with ice/salt bath under N, purge. Slowly add 2.55 gms potasslum t-butoxide (0.227 mole Aldrich 15,667-1). After addition is complete, continue to stir at -10°C monitoring by TLC. Once reaction is complete, quench by adding 135 mls 10% HCl stirring 10 min. Extract three times with ether. Dry organic layer with MgSO,, filter and rotovap to dryness. Crystallize from ether. Obtain NMR and mass spec (m/z=474).

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Step 7

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Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N, inlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N, purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

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C17H39NO4S fw=473.68

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Chill solution with ice bath. Quench with 100 mls 10% K₁CO, while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl, once H₂O, and once with saturated NaCl solution. Dry organic layer with MgSO,, filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec (m/z-460).

Step 4

C35H33NO6S fw=475.61

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mass spec (m/z=476). dry with MgSO. Filter and rotovap to dryness. Obtain night in freezer. Filter solid from reaction, extract 8 hrs to convert to the sulphone. Chill solution over goes quickly to the sulphoxide intermediate but takes chloroperbenzoic acid (0.0435 moles, Fluka 25800, ml round bottom flask with magnetic stir bar. Fit isolating by column chromatography. Obtain NMR and pure product by crystallizing from ethanol or with methylene choride. filtrate with 10% K2CO3. temperature and monitor reaction by TLC. Reaction ~65%). After addition is complete warm to room ice bath under N, purge. Slowly add 11.54 gms 3flask with N, inlet and stopper. Chill solution with 120 mls anhydrous methylene chloride. Place in a 250 Dissolve 9.33 gms (0.021 moles) of product 3 with Extract aqueous layer twice Combine organic layers and

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Step 5

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C27H1,NO.S

fw=473.68

stir rate of 250 rpm. Run overnight under these under H_2 . Run reaction at 200 psig H_3 , 55°C, and a bag. Purge reactor three times with H₂. Heat to 55°C wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 atmosphere glove bag. In glove bag, add 15.3 mls For safety reasons next two compounds are added in a N_1 of product 4 in reactor base. Add 160 mls ethanol. stirred mini reactor. Place 9.68 gms (0.0204 moles) conditions. 20,569-9). Seal reactor before removing from glove Reaction is done in a 300 ml stainless steel Parr

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rotovap to dryness. Dry on vacuum line. water. Dry organic layer with MgSO, filter and mixture over a bed of celite washing well with ether. progress of run by TLC. Reaction is a mixture of desired product and intermediate. Filter reaction Rotovap and redissolve with ether. Extract with Charge reactor again with same amounts, seal Cool reactor and vent H2. Purge with N3. Check

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converted to the desired product. Cool and vent H, After second run all of the material has been reactor and run overnight under same conditions.

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inlet, addition funnel and stopper. Stir with magnetic benzophenone from step 1 in 250mls anhydrous methylene chloride. Place in a 3 liter flask fitted with N2 stir bar. Chill solution with ice bath.

Prepare a solution of 39.32 gms trifluoromethane sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N2. Stir 5 minutes after addition is complete.

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dropwise to chilled solution under N,. Stir 5 minutes Place in addition funnel and add Prepare a solution of 22.85 gms triethyl silane (0.197mole Aldrich 23,019-7) and 170mls anhydrous after addition is complete. methylene chloride.

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methylene chloride. Place in addition funnel and add dropwise to chilled solution under N. Stir 5 minutes trifluoromethane sulfonic acid and 170mls anhydrous Prepare a second solution of 39.32 gms after addition is complete.

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silane and 170mls anhydrous methylene chloride. Place solution under N_2 . After all additions are made allow Prepare a second solution of 22.85 gms triethyl to slowly warm to room temperature overnight. Stir in addition funnel and add dropwise to chilled under N, overnight.

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organic layer and extract aqueous layer 2 times with Crystallize from ethanol. Dry on vacuum line. Dry Prepare 1300 mls saturated NaHCO, in a 4 liter *t=28.8gms. Confirm by NMR and mass spec (m/z=278). methylene chloride. Dry organic layers with MgSO. vigorously, slowly add reaction mixture. Stir at separatory funnel and allow separation. Remove beaker. Chill with ice bath. While stirring chilled temperature for 30 min. Pour into a

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Step 3

C25H13NO4S fw=443.61

Li₂S (0.040 moles Aldrich 21,324-1). Place flask in oil bath and heat at 75°C under N, overnight then cool with 200 mls anhydrous DMSO. Place in a 500 ml round water condenser, N, inlet, and stopper. Add 1.84 gms bottom flask with magnetic stir bar. Fit flask with Dissolve 10.12 gms (0.036 moles) of product 2 to room temperature.

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reaction solution. Purge well with N, heat overnight moles). Dissolve with anhydrous DMSO and add to Weigh out 10.59 gms dibutyl mesylate (0.040 at 80°C.

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MgSO,, filter and rotovap to dryness. Dry oil on vacuum with ether 3 times. Combine organic layers and extract Cool to room temperature. Prepare 500 mls of 5% slowly add reaction mixture. Stir 30 min. Extract using 95% hexane and 5% ethyl acetate as the mobile Obtain pure product by column chromatography with water and sat'd NaCl. Dry organic layer with phase. Dry wt=7.8 gms. Obtain NMR and mass spec acetic acid in a 2 liter beaker. While stirring, (m/z=444).

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chromatography (Waters Delta Prep 3000) using an acetonitrile /water gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of 7 as a white foam. ¹H NMR (CDCl₃) d 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.6 Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J = 1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed 642.4343.

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Example 1398a

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Step 1

C14H10ClNO, fw=291.69

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In an inert atmosphere, weigh out 68.3 gms phosphorus pentachloride (0.328mole Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Pit flask with a N₂ inlet adapter and suba seal. Remove from inert atmosphere and begin N₂ purge. Add 50mls anhydrous chlorobenzene (Aldrich 28,451-3) to the PC1, via syringe and begin stirring with magnetic stir bar

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Weigh out 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3). Slowly add to the chlorobenzene solution while under N, purge. Stir at

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room temperature overnight. After stirring at room temperature for -20hrs, place in oil bath and heat at 50C for 1hr. Remove chlorobenzene by high vacuum. Wash residue with anhydrous hexane. Dry acid chloride wt=61.95gms. Store in inert and dry atmosphere.

In inert atmosphere, dissolve acid chloride with 105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask.

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Weigh out 45.1gms aluminum chloride (0.34 moles Aldrich 29,471-3) and place in a solid addition funnel. Pit reaction flask with addition funnel and a N, inlet adapter. Remove from inert atmosphere. Chill reaction solution with ice bath and begin N, purge. Slowly add AlCl, to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight.

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Quench reaction by pouring into a solution of 300 mls in HCl and ice. Stir 15 min. Extract twice with ether. Combine organic layers and extract twice with 2% NaOH, then twice with deionized H₂O. Dry with MgSO₄, filter and rotovap to dryness. Remove anisole by high vacuum. Crystalize product from 90% ethanol 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms. Yield 41%. Obtain NMR and mass spec (m/z=292).

Step 2

Dissolve 38.10gms (0.131 moles) of the

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Step 5. Preparation of 5

filtrate was concentrated in vacuo to give 0.9 g (96%) sealed, purged twice with H,, then charged with H, (100 6H), 3.07 (QAB, JAB = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 of 5. ¹H NMR (CDCl,) d 0.80-0.98 (m, 6H), 1.00-1.52 (m, 8.9 Hz, 1H). MS(FABH⁺) m/e (relative intensity) 459.7 ethanol in a stainless steel Parr reactor was added 1 Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, psi) and heated to 45 °C for six hours. The reaction (8, 2H), 4.14 (8, 1H), 5.43 (8, 1H), 6.09 (d, J = 2.4 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = g 10% palladium on carbon. The reaction vessel was J = 7.8 and 1.8 Hz, 1H), 6.83 (8, 1H), 6.93 (d, J = To a suspension of 1.0 g (2.1 mmol) of 4 in 100 ml vessel was cooled to ambient temperature and the (100). HRMS calculated for M+H 459.2681. Found contents filtered to remove the catalyst. The

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Step 6. Preparation of 6

Next was added 4 g (39.6 mmol) TEA. The reaction was using a gradient of ethyl acetate(20-50%) in hexane as silica gel chromatography through a 70 ml MPLC column eluent yielded 0.9 g (73%) of 6 as a pale yellow oil. 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 6.9 Hz, 2H), 4.10 (8, 1H), 5.51 (8, 1H), 5.95 (d, J = was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride. (qAB, JAB = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = '8, 1H), 7.32-7.41 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), To a solution of 914 mg (2.0 mmol) of 5 in 50 ml THF 2.4 Hz, 1H), 6.51 (dd, J = 9.3 and 2.7 Hz, 1H), 7.28 Purification by stirred 10 minutes, then partitioned between ethyl ¹H NMR (CDCl₃) d 0.84-0.95 (m, 6H), 1.02-1.53 (m, The organic layer was dried (MgSO,) and concentrated in vacuo. 7.90 (d, J = 9.0 Hz, 1H). acetate and brine.

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Step 7. Preparation of 7

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To a solution of 0.9 g (1.45 mmol) of 6 in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Purification by reverse-phase silica gel

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Step 3. Preparation of 3

9.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). 1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J = 6.0 Hz, 1H), 5.67 (s, 1H), 6.34 (dd, J=9.6 and 3.0 Hz eluent yielded 4.3 g (90%) of 3 as a pale yellow foam chromatography through a 100 ml plug using CH2Cl, as and concentrated in vacuo. Purification by silica gel organic layer was washed with brine, then dried (MgSO,) partitioned between ethyl acetate and water; the of saturated ammonium chloride. The mixture was 30 minutes, then the reaction was quenched with 100 mL the temperature at <5 °C. Stirring was continued for of potassium t-butoxide was added slowly, maintaining cooled to 0 °C in an ice bath. 20 mL of a 1 M solution A solution of 4.8 g (10.4 mmol) of 2 in 500 mL THF was 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 1 H NMR (CDCl₃) d 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 $(q_{AB}, J_{AB} = 15.0 \text{ Hz}, \Delta V = 33.2 \text{ Hz}, 2H), 4.17 (d, J = 1.00)$ (65). HRMS calculated for M+H 464.1907. Found MS(FABH+) m/e (relative intensity) 464.5 (100), 446.6

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Step 4. Preparation of 4

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= 9.0 Hz, 1H), 5.65 (8, 1H), 5.75 (d, J = 2.1 Hz, 1H) $3.09 (q_{AB}, J_{AB} = 15.0 \text{ Hz}, DV= 45.6 \text{ Hz}, 2H), 4.90 (d, J)$ 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), NMR (CDCl₃) d 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), an ethyl acetate/hexanes gradient (10-40% ethyl by silica gel chromatography (Waters Prep-2000) using and the contents concentrated in vacuo. Purification The reaction vessel was cooled to ambient temperature vessel was sealed and heated to 110 °C for 16 hours. vessel was added 8.2 g dimethyl amine (182 mmol). The 3 in 30 ml THF contained in a stainless steel reaction Hz, 1H), 8.20 (dd, J=8.4 and 1.2 Hz, 1H), 8.43 (s, Hz, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.0 6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4471.5 (25). HRM9-calculated for M+H 489.2423. Found 1H). MS(FABH+) m/e (relative intensity) 489.6 (100) acetate) gave 4.0 g (88%) of 4 as a yellow solid. H 489.2456. To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of

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vacuum to give 11.9 g (yield 74%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

Step 2: 2-[2-4'-methoxybenzyl-4-nitrophenylthio)methyl]-2-butylhexanal:

chloride, filtered through silica gel, eluted with 20% mmole) in 50 ml methylene chloride cooled in ice bath mmole). The reaction was stirred for 18 hours at room dried over magnesium sulphate, and concentrated under To a solution of the hexanol of step 1 (6 g, 13 vacuum to give 5 g (yield 77.7%) of the hexanal as a white solid, MP 58-60°C. Proton NMR, C13-NMR and MS vacuum. The concentrate was dissolved in methylene cemperature and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, ethyl acetate and hexane, and concentrated under under nitrogen was added 70% MCPBA (8,261 g, 33 confirmed the product.

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Example 1398

Step 1. Preparation of 2

organic layer was dried over MgSO, and concentrated \underline{in} (Waters Prep-2000) using ethyl acetate/hexanes (25/75) tetrakis (triphenylphosphine) palladium(0) (0.7 mmol) 2H), 3.20 (8, 2H), 4.59 (s, 2H), 6.93 (dd, J = 10.5 and 2.4 Hz, 1H), 7.15 (dt, J = 8.4 and 2.85 Hz, 1H), This heterogeneous mixture was refluxed for three hours, then cooled to ambient temperature and 0.99-1.38 (m, 8H), 1.62-1.75 (m, 2H), 1.85-2.00 (m, and 45 mL of a 2 M solution of sodium carbonate in dialdehyde of Example 1395 (14.3 mmol) in 72 mL of gave 4.8 g (73%) of the title compound as a yellow H NMR (CDC1,) d 0.88 (t, J = 7.45 Hz, 6H), To a solution of 6.0 g of dibutyl 4-fluorobenzene Purification by silica gel chromatography partitioned between ethyl acetate and water. The toluene and 54 mL of ethanol was added 4.7 g 3nitrobenzeneboronic acid (28.6 mmol), 0.8 g of water. solid. vacuo.

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7.46-7.59 (m, 2H), 8.05-8.16 (m, 3H), 9.40 (s, 1H).

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filtered. The filtrate was washed successively with 10% NaOH(3X), water, and brine, dried over magnesium sulphate, and concentrated under vacuum to give 0.42 g (yield 90%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

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Step 7: Cis-3,3-dibutyl-7-methyl-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide:

solid. Proton NMR, carbon NMR and MS confirmed the and concentrated under vacuum. This concentrate was product. (M+H=433). purified by HPLC (10% EtOAc-Hexane). The first successively with water and brine, dried with MgSO, (75% yield) of the desired benzothiepine as a white form of an oil. The second fraction yielded 0.27 g fraction came as 0.1 g of the starting material in the with 10% HCl, extracted with ether, washed material. The crude reaction mixture was acidified of the product and a small amount of the starting hours thin layer chromatography confirmed the presence mmole) in 30 ml of anhydrous THF was stirred in an ice butoxide (102 mg, 0.85 mmole) was then added. After 3 bath at a temperature of about 0°C. Potassium-tert-A mixture of the hexanal of step 6 (0.37 g, 0.85

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Example Corresponding to Scheme XII

Step 1: 2-[(2-4'-methoxybenzyl-4-nitrophenylthio)methyl]-2-butylhexanol:

$$O_{2N}$$
 S
 B_{U}
 $O_{CH_{3}}$
 B_{U}

and brine, dried over magnesium sulphate, and Step 3 of the Scheme XI examples) in 10 ml of DMF was overnight. The solution was cooled to 0°C and ml of DMF and lithium sulfide [1.75 g, 1.05 ethyl acetate and hexane, and concentrated under chloride, filtered through silica gel, eluted with 20% vacuum. The concentrate was dissolved in methylene over magnesium sulphate, and concentrated under and extracted with ethyl acetate. The organic layer with 3M of NaOH for 1 hour. The mixture was cooled The organic layer was washed successively with water mixture was cooled and extracted with ethyl acetate. added and the reaction mixture boiled overnight. The separated and 40 ml of concentrated sulfuric acid was water and ether (three times). The water layer was solvent was evaporated and washed successively with added and stirred at room temperature overnight. The dibutyl-cyclic-sulfate (9.9g; prepared as set forth in red. The reaction mixture was heated at 80°C equivalents] was added. The solution color changed to was washed successively with water and brine, dried concentrated under vacuum. Chlorodiphenylmethane (10g) was dissolved in 25 The product was boiled

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Step 4: 2-[(2-4'-fluorobenzyl-4-methylphenylthio) methyl]-2-butylhexanol:

the washed sodium hydride and cooled in an ice bath. A ether two times. The water layer was separated and 20 and boiled for 10 minutes. The mixture was cooled and decanted and 20 ml of methoxyethyl ether was added to A 60% oil dispersion of sodium hydride (0.27 g, The solvent was evaporated and washed with water and Gas chromatography confirmed there was no thiol left. umole) in 10 ml of methoxyethyl ether was then added. The resulting mixture was stirred for 30 minutes at boiled for 30 minutes, cooled, acidified with 6N HCI, nagnesium sulphate, and concentrated under vacuum to 6.68 mmole) was washed with hexane. The hexane was mixture of diphenylmethane thiophenol (1.55 g, 6.68 dropwise over a period of 15 minutes. A mixture of ml of 10% NaOH was added. This aqueous mixture was extracted with ether. The organic layer was washed the dibutyl-cyclic-sulfate of step 3 (2.17 g, 8.66 give 2.47 g (yield 92.5%) of the hexanol as an oil. 0°C and 1 hour at room temperature under nitrogen. Proton NMR, Cl3-NMR and MS confirmed the product. mmole) in 10 ml of methoxyethyl ether was added successively with water and brine, dried over

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Step 5: 2-[(2-4'-fluorobenzyl-4methylphenylthio)methyl]-2-butylhexanal:

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To a solution of the hexanol of step 4 (2 g, 4.9 mmole) in 40 ml of methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmole). The reaction mixture was stirred for 3 hours and filtered through silica gel. The filtrate was concentrated under vacuum to give 1.39 g (yield 70%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the

Step 6: 2-[(2-4'-fluorobenzyl-4-methylphenylsulfonyl)
methyl]-2-butylhexanal

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product.

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To a solution of the hexanal of step 5 (0.44 g, 1.1 mmole) in 20 ml of methylene chloride cooled by an ice bath under nitrogen was added 70 % metachloroperbenzoic acid (0.54 g, 2.2 mmole). The reaction mixture was stirred for 18 hours and

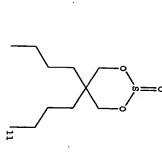
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of the diol as an oil. Proton NMR, carbon NMR and $\ensuremath{\mathsf{MS}}$ confirmed the product.

Step 2: Dibutyl-cyclic-sulfite:



A solution of the dibuty1-diol of step 1 (103 g, 0.5478 mol) in anhydrous methylene chloride (500 ml) and triethylamine (221 g, 4 equivalents, 2.19 mol) was stirred at 0°C under nitrogen. Thionyl chloride (97.78 g, 0.82 mol) was added dropwise to the mixture. Within 5 minutes the solution turned to yellow and then to black when the addition was completed within about half an hour. The reaction was completed within 3 hours (gas chromatography confirmed no starting material was left). The mixture was washed with ice waser twice, and brine twice. The organic phase was dried over magnesium sulphate and concentrated under vacuum to give 128 g (yield 100%) of the dibuty1-cyclic-sulfite as a black oil. NMR and MS were consistent with the product.

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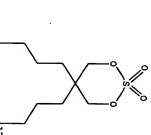
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Step 3: Dibutyl-cyclic sulfate:



To a solution of the dibutyl-cyclic-sulfite of step 2 (127.5 g, 0.54 mol) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium(III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. Gas chromatography confirmed there was no starting material left. The mixture was extracted once with 300 ml of ether and three times with brine. The organic phase was dried over magnesium sulphate and passed through celite. The filtrate was concentrated under vacuum and gave 133 g (yield 97.8%) of the dibutyl-cyclic-sulfate as an oil. Proton NMR, carbon NMR and MS confirmed the product.

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of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield a mixture of an ester and alcohol LI. Sultable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid. The ester is then converted to alcohol LI by treatment with an alkali metal hydroxide, preferably sodium hydroxide.

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The several reactions involving halobenzene L, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need to isolate any of the intermediates produced.

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Alcohol LI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to sulfone-alcohol LII. Preferably, the oxidizing agent is metachloroperbenzoic acid. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

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Sulfone-alcohol LII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde LIII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

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Sulfone-aldehyde XLIII is then converted to the desired benzothiepine-1,1-dioxides according to the procedure previously set forth in Scheme XI.

The two oxidation steps can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield an aldehyde which is then oxidized to yield a sulfone-aldehyde.

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Use of the cyclic sulfate reagent instead of a mesylate reagent in Schemes XI and XII improves the overall yield and avoids many of the purification

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difficulties encountered relative to those reaction schemes proceeding through a mesylate intermediate. Overall yields are significantly improved when a cyclic sulfate is used instead of a mesylate reagent. In addition, chromatographic separation of the intermediate product of the cyclic sulfate coupling step of the reaction is not necessary. For example, in Schemes XI and XII the intermediate is a water soluble alkali metal salt and the impurities can be removed by extraction with ether. The intermediate is then hydrolyzed to the desired alcohol.

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Example Corresponding to Scheme XI:

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Step 1: Preparation of 2,2-dibutyl-1,3-propanediol:

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OH OH

Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyl-

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diethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated under vacuum to give 98.4 g (yield 95%)

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Halobenzene L (which is commercially available or can be synthesized from commercially available halobenzenes by one skilled in the art) has the following formula:

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wherein R³, R⁴, and g are as previously defined for the compounds of formula I; R^h is a halogen such as chloro, bromo, fluoro or iodo; and R⁴ is an electron withdrawing group at the ortho or para position of the halobenzene, and is preferably a p-nitro or o-nitro group. Cyclic sulfate XL can be prepared as set forth in Scheme XI and can have the following formula:

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wherein R' and R' are as previously defined for the compounds of formula I. Preferably, R' and R' are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R' and R' are n-butyl.

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In the process of Scheme XII, halobenzene L is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as dimethyl formamide or N:N-dimethylacetamide, and more preferably, in dimethyl formamide. Although the reaction conditions such as temperature and time

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are not narrowly critical, the reaction preferably is allowed to proceed at between about 70°C and about 90°C for about 8 to 12 hours. More preferably, the reaction temperature is maintained at about 80°C. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield is improved by using about 1.1 to 1.3 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present.

of halobenzene L present. equivalents of abstracting agent for each equivalent relative to halobenzene L. Reaction time and yield is slight excess of the abstracting agent is preferred present. More preferably, this ratio is about 1.05 abstracting agent for each equivalent of halobenzene L improved by using about 1.01 to 1.3 equivalents of sulfide, and preferably it is dilithium sulfide. A abstracting agent generally is a dialkali metal of the open ring sulfate is the sulfate group. ring sulfate. The terminal group at the unbonded end sulfate ring. The sulfur anion of the halobenzene sulfur anion reacts with cyclic sulfate XL to open the atom with a divalent sulfur atom. The resulting or after the addition of cyclic sulfate XL. Without abstracting agent can be added to the solvent then bonds with a terminal carbon atom of the open the benzene ring of halobenzene L and replaces that abstracting agent removes the halogen atom attached to being held to a particular theory, it is believed the containing halobenzene L prior to, concurrently with also is treated with an abstracting agent. The In the process of the invention, halobenzene L

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The sulfate group of the product of the reaction

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a sulfone-alcohol which is then oxidized to yield a sulfone-aldehyde.

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113 Scheme XII

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Scheme XII illustrates still another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl analogs, starting from the halobenzene L. Halobenzene L can be reacted with cyclic sulfate XL disclosed above to give the alcohol LI which can be oxidized to yield the sulfone-alcohol LII. Sulfone-alcohol LII itself can be further oxidized to give the sulfone-aldehyde LIII which can be cyclized to give a stereoisomeric mixture of benzothiepine LIVa and LIVb.

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equivalent of thiophenol XVIIIA present. 1.1 equivalents of cyclic sulfate XL for each XVIIIA present. More preferably, this ratio is about cyclic sulfate XL for each equivalent of thiophenol being preferred. Reaction time and yield can be materials, with a slight excess of cyclic sulfate XL approximately stoichiometric ratio of the starting improved by using about 1.01 to 1.3 equivalents of hours. The reaction preferably employs an to proceed at about room temperature for about two narrowly critical, the reaction preferably is allowed conditions such as temperature and time are not

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group. atom from the mercaptan group attached to the benzene unbonded end of the open ring sulfate is the sulfate the open ring sulfate. The terminal group at the of the thiophenol then reacts with cyclic sulfate XL ring of thiophenol XVIIIA. The resulting sulfur anion believed the abstracting agent removes the hydrogen containing thiophenol XVIIIA prior to, concurrently XVIIIA also is treated with an abstracting agent. thiophenol then bonds with a terminal carbon atom of to open the sulfate ring. The sulfur anion of the Without being held to a particular theory, it is with, or after the addition of cyclic sulfate XL abstracting agent can be added to the solvent In the process of the invention, thiophenol The

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a pH greater than about 10. Preferably, the base is an alkali metal hydride such as sodium hydride, about 1.0 to about 1.1 equivalents of abstracting XVIIIA. Reaction time and yield is improved by using agent for each equivalent of thiophenol XVIIIA abstracting agent is preferred relative to thiophenol the base is sodium hydride. A slight excess of lithium hydride or potassium hydride; more preferably, The abstracting agent generally is a base having

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of thiophenol XVIIIA present. equivalents of abstracting agent for each equivalent present. More preferably, this ratio is about 1.1

sulfuric acid. mineral acids, particularly hydrochloric acid and alcohol XLI. Suitable hydrolyzing agents include XL is then removed, preferably by hydrolysis, to yield the reaction of thiophenol XVIIIA with cyclic sulfate The sulfate group of the intermediate product of

produced. the need for isolation of any of the intermediates the hydrolyzing agent can take place in situ without XVIIIA, cyclic sulfate XL, the abstracting agent and The several reactions involving thiophenol

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solvent such as methylene chloride or chloroform. and more preferably, it is pyridinium chlorochromate. agent is sulfur trioxide or pyridinium chlorochromate, agents to aldehyde XLII. Preferably, the oxidizing salicylate) and oxidized using standard oxidizing methods (for example, extraction with aqueous methyl The reaction is conducted in a suitable organic Alcohol XII is then isolated by conventional

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oxidizing agent is metachloroperbenzoic acid. agents to sulfone-aldehyde XLIII. Preferably, the methods and further oxidized using standard oxidizing Aldehyde XLII is then isolated by conventional

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between about 8 and about 9. More preferably, the cyclizing agent preferably is a base having a pH the base is potassium tert-butoxide. base is an alkoxide base, and still more preferably, conventional methods and then cyclized to form the stereoisomeric benzothiepines XLIVa and XLIVb. The Sulfone-aldehyde XLIII likewise is isolated by

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reversed without adversely affecting the overall reaction. The two oxidation steps of Scheme XI can be Alcohol XLI can be oxidized first to yield

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SCHEME XI.

SOCI2

RIPA

RUCI, Nalo,

OH

(R⁸)_q (R⁸)

3. H2SO4

Koußu (R*)_q + + (R*)_q OH (R*)_q OH

XLIVa ASTAN

Scheme XI illustrates yet another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl

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analogs, starting from the thiophenol XVIIIA. Thiophenol XVIIIA can be reacted with cyclic sulfate XL to give the alcohol XLI which can be oxidized to yield the aldehyde XLII. Aldehyde XLII itself can be further oxidized to give the sulfone XLIII which can be cyclized to give a stereoisomeric mixture of benzothiepine XLIVa and XLIVb.

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Thiophenol XVIIIA can be prepared according to Scheme 3 as previously discussed and has the following formula:

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XVIIIA

wherein R's R* and q are as previously defined for the compounds of formula I. Cyclic sulfate XL can be prepared according to synthetic procedures known in the art and has the following formula:

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X

wherein R¹ and R² are as previously defined for the compounds of formula I. Preferably, R¹ and R³ are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R¹ and R² are n-butyl.

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In the process of Scheme XI, thiophenol XVIIIA is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as methoxyethyl ether. While the reaction

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MCPBA

MCPBA = m-chloroperbenzoic acid

R⁵B(OR)₂, heat

$$R^3SnR_3$$
, heat
$$Pd(Ph_3P)_A$$
, solvent
$$R = H$$
, or $C_1 \cdot C_6$ alky!

10 sulfide to sulfone yielded the key intermediate W. alcohol to benzyl bromide, followed by oxidation of reduction of the dialdehyde at low temperature yielded provided a dialkyl benzene dialdehyde Y. DIBAL by the addition of dialkyl mesylate aldehyde (\mathbf{X}) , polar solvent (such as DMF, DMA, DMSO, etc.), followed lithium sulfide or other nucleophilic sulfide anion in appropriately substituted 2-fluorobenzaldehyde with Generic Scheme X: The nucleophilic substitution of an benzyl alcohol monoaldehyde Z. Conversion of benzyl

the cyclic sulfate as the reagent. reagent as shown in the following schemes XI and XII. synthesized using cyclic sulfate (XL, below) as the The following examples describe a procedure for using The compounds of this invention can also be

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Scheme 6

$$\sum_{\substack{P_1 \\ P_2 \\ NO_2}} R^2 \qquad H_2 \cdot PdJC \qquad H^2 \\ R^6 CH_2 OH \qquad O_2 S \qquad NH$$

potassium t-butoxide, THF

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EXAMPLES OF SYNTHETIC PROCEDURES

Preparation 1

2-Ethyl-2-(mesyloxymethyl)hexanal (1)

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To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of triethylamine was added dropwise 15.8 g of 2-ethyl-2-(hydroxymethyl)hexanal, prepared according to the procedure described in Chem. Ber. 98, 728-734 (1965), while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with dilute HCl and extracted with methlyene chloride. The methylene chloride extract was dried over MgSO, and concentrated in vacuo to give 24.4 g of brown oil.

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Preparation 2

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2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

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A mixture of 31 g (0.144 mol) of 2mercaptobenzophenone, prepared according to the
procedure described in W0 93/16055, 24.4 g (0.1 mole)
of 2-ethyl-2-(mesyloxymethyl)-hexanal (1), 14.8 g
(0.146 mole) of triethylamine, and 80 mL of 2methoxyethyl ether was held at reflux for 24 h. The
reaction mixture was poured into 3N HCl and extracted
with 300 mL of methylene chloride. The methylene
chloride layer was washed with 300 mL of 10% NaOH,
dried over MgSO, and concentrated in vacuo to remove 2methoxyethyl ether. The residue was purified by HPLC
(10% EtOAc-hexane) to give 20.5 g (58%) of 2 as an

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solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

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sodium chloride solution. In addition, sterile, fixed diglycerides. In addition, fatty acids such as oleic formulated according to the known art using suitable for example, as a solution in 1,3-butanediol. Among suspending medium. For this purpose any bland fixed injectable aqueous or oleaginous suspensions may be nontoxic parenterally acceptable diluent or solvent, dispersing or setting agents and suspending agents. employed are water, Ringer's solution, and isotonic Injectable preparations, for example, sterile The sterile injectable preparation may also be a the acceptable vehicles and solvents that may be oils are conventionally employed as a solvent or oil may be employed including synthetic mono- or acid find use in the preparation of injectables. sterile injectable solution or suspension in a

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Pharmaceutically acceptable carriers encompass all the foregoing and the like.

Treatment Regimen

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The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological

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considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

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levels by any of the methods well known in the art, to so that the duration of treatment can be determined as schedule can be rationally modified over the course of monitored by, for example, measuring serum cholesterol continued as necessary over a period of several weeks nvention are administered at any point in time, and therapy so that the lowest amount of ileal bile acid and so that administration is continued only so long disease condition has been controlled or eliminated. to several months or years until the hyperlipidemic Patients undergoing treatment with the compounds or exhibits satisfactory effectiveness is administered, hyperlipidemic condition can begin with the dosages Initial treatment of a patient suffering from determine the effectiveness of therapy. Continuous transport inhibitor of the present invention which analysis of such data permits modification of the well. In this way, the treatment regimen/dosing treatment regimen during therapy so that optimal indicated above. Treatment should generally be compositions disclosed herein can be routinely effective amounts of compounds of the present as is necessary to successfully treat the hyperlipidemic condition.

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The following non-limiting examples serve to illustrate various aspects of the present invention.

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inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

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Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

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pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

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Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

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pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active

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compound is generally present at a concentration of . from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

15 10 U electrotransport or iontophoresis, for example, as or dispersed in a polymer. A suitable concentration (1986). described in Pharmaceutical Research, 3(6), 318 compound can be delivered from the patch by of the active compound is about 1% to 35%, preferably present invention in an optionally buffered, aqueous time. Such patches suitably contain a compound of the about 3% to 15%. As one particular possibility, the solution, dissolved and/or dispersed in an adhesive, epidermis of the recipient for a prolonged period of adapted to remain in intimate contact with the administration can be presented as discrete patches Pharmaceutical compositions suitable for transdermal Transdermal administration is also possible.

In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

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The solid dosage forms for oral administration including capsules, tablets, pills, powders, and granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

35 Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions,

formulations, as are well known in the art, to provide physical properties of the formulation, bioadhesion of phthalate, hydroxypropylmethylcellulose phthalate and drug from the dosage form. The intended effect is to release from the dosage form based on the changing pH intestinal tract, or enzymatic release of the active anionic polymers of methacrylic acid and methacrylic enteric-coated and enteric-coated controlled release These include, but are not limited to, pH sensitive of the small intestine, slow erosion of a tablet or gastrointestinal tract by any number of mechanisms. prolonged or sustained delivery of the drug to the Oral delivery of an ileal bile acid transport extend the time period over which the active drug molecule is delivered to the site of action (the formulations are within the scope of the present inhibitor of the present invention can include sapsule, retention in the stomach based on the .nvention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate the dosage form to the mucosal lining of the ileum) by manipulation of the dosage form. acid methyl ester.

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When administered intravenously, the dose can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight to about 0.75 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg

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per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

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or non-aqueous liquid; or as an oil-in-water or water-Compressed tablets then, if necessary, shaping the product. For example, can be prepared by compressing, in a suitable machine, or granules optionally mixed with a binder, lubricant, in-oil emulsion. As indicated, such compositions can such as capsules, cachets, lozenges, or tablets, each granules; as a solution or a suspension in an aqueous the compound in a free-flowing form, such as a powder a tablet can be prepared by compressing or molding a liquid or finely divided solid carrier, or both, and be prepared by any suitable method of pharmacy which powder or granules of the compound, optionally with general, the compositions are prepared by uniformly Includes the step of bringing into association the and intimately admixing the active compound with a Pharmaceutical compositions suitable for oral administration can be presented in discrete units, containing a predetermined amount of at least one compound of the present invention; as a powder or constitute one or more accessory ingredients). active compound(s) and the carrier (which can one or more assessory ingredients.

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mammal, e.g., a human. action in the body, for example in the ileum of a

present invention can be used as the compound per se conditions referred to above, the compounds of the For the prophylaxis or treatment of the

methanesulfonic, succinic, toluenesulfonic, tartaric, potassium salts, and alkaline earth salts such as pharmaceutically acceptable base salts include and trifluoroacetic acids. The chloride salt is citric, ethanesulfonic, fumaric, gluconic, glycolic, pharmaceutically acceptable acid addition salts of the pharmaceutically acceptable anion or cation. Suitable particularly suitable for medical applications because particularly preferred for medical purposes. Suitable acids such as acetic, benzenesulfonic, benzoic, nitric, sulfonic, and sulfuric acids, and organic compounds of the present invention when possible parent compound. Such salts must clearly have a of their greater aqueous solubility relative to the ammonium salts, alkali metal salts such as sodium and isothionic, lactic, lactobionic, maleic, malic, hydrochloric, hydrobromic, phosphoric, metaphosphoric, include those derived from inorganic acids, such as

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the above list. pharmaceutically acceptable and are also selected from invention are, of course, also required to be The anions of the definition of A' in the present

presented with an acceptable carrier in the form of a not be deleterious to the recipient. pharmaceutical composition. The carrier must, of be a solid or a liquid, or both, and is preferably The carrier can

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Pharmaceutically acceptable salts are

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magnesium and calcium salts.

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The compounds of the present invention can be

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with the other ingredients of the composition and must course, be acceptable in the sense of being compatible

> admixing the components. techniques of pharmacy, consisting essentially of invention can be prepared by any of the well known invention. The pharmaceutical compositions of the present, including other compounds of the present Other pharmacologically active substances can also be from 0.05% to 95% by weight of the active compound. composition, for example, a tablet, which can contain formulated with the compound as a unit-dose

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compounds or as a combination of therapeutic compounds. with pharmaceuticals, either as individual therapeutic conventional means available for use in conjunction These compounds can be administered by any

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compound chosen, the use for which it is intended, the the recipient. mode of administration, and the clinical condition of depend on a number of factors such as the specific achieve the desired biological effect will, of course, The amount of compound which is required to

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preferably from about 1 mg to about 50 mg/kg sustained release form effective to obtain desired proportionate multiple subdoses. Subdoses can be 10 mg/kg bodyweight/day. This total daily dose can be administered 2 to 6 times per day. Doses can be in administered to the patient in a single dose, or in bodyweight/day, more preferably from about 3 to about from about 0.3 to about 100 mg/kg bodyweight/day, In general, a daily dose can be in the range of

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preferably from about 10 to about 50 mg of compound. preferably about 1 to about 75 mg of compound, more about 0.1 to about 100 mg of benzothiepine compound, In the case of pharmaceutically acceptable salts, the as tablets or capsules, can contain, for example, from Orally administrable unit dose formulations, such

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N, and

 $R^{\star s}$ and $R^{\star r}$ are independently selected from the group consisting of:

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wherein R³⁴, R³⁹ and R³¹ are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

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A' is a pharmaceutically acceptable anion, and k = , , , ,

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In compounds of Formula DIV, R²⁰, R²¹, R²² in Formulae DII and DIII, and R²¹ in Formula DIII can be bonded at any of their 6-, 7-, 8-, or 9- positions to R¹⁹. In compounds of Formula DIVA, it is preferred that R³⁵ comprises a phenylene moiety bonded at a m- or p-position thereof to R¹⁹.

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In another embodiment, a core moiety backbone, R^{19} , as discussed herein in Formulas DII and DIII can be multiply substituted with more than four pendant active benzothiepine units, i.e., R^{19} , R^{11} , R^{21} , and R^{21} as discussed above, through multiple functional groups

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active benzothiepine units within a single core moiety within any of the groups encompassed by the definition about one to about 100, preferably about one to about individual core moiety backbone units can range from backbone unit, R19, can comprise a single core moiety points of attachment of similar or different pendant more preferably about one to about 25. The number of 80, more preferably about one to about 50, and even backbone unit can be in the range from about one to unit, multimers thereof, and multimeric mixtures of the different core moiety units discussed herein, about 100, preferably about one to about 80, more preferably about one to about 25. Such points of within the core moiety backbone. The core moiety attachment can include bonds to C, S, O, N, or P preferably about one to about 50, and even more i.e., alone or in combination. The number of

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The more preferred benzothiepine moieties comprising R²⁰, R²¹, R²¹ and/or R²¹ conform to the preferred structures as outlined above for Formula I.

The 3-carbon on each benzothiepine moiety can be achiral, and the substituents R¹, R², R³, R⁴, R⁴ and R⁵ can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(exyalkylene) or oligo(exyalkylene) or oligo(exyalkylene) or poly- or oligo(exyethylene) or poly- or

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Dosages, Formulations, and Routes of Administration

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The ileal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of

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quatarnary heterocycle, quaternary heteroaryl, or SO, SO2, S'R'R', PR7, P+R7R8, phenylene, heterocycle, have one or more carbon replaced by O, NR', N'R'R', S amino acid, and peptide polypeptide, can optionally diyl, polyether diyl, polyalkoxy diyl, carbohydrate

S'R"R"A', and N+R9R11R12A-; C(0)OM, COR^{13} , $P(0)R^{13}R^{14}$, $P^{\dagger}R^{13}R^{14}R15A$ -, $P(OR^{13})OR^{14}$ NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$ SR^{13} , $S(0)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$ heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴ polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, group consisting of alkyl, alkenyl, alkynyl, and polypeptide can be substituted with one or more polyalkoxy diyl, carbohydrate, amino acid, peptide, polyalkane diyl, alkoxy diyl, polyether diyl, substituent groups independently selected from the wherein alkane diyl, alkene diyl, alkyne diyl,

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 $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$, and alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, CO_2R^7 , CN, oxo, CONR^7R^8 , $\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$, alkyl, alkenyl, polyether, aryl, haloalkyl, cycloalkyl, and consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 more substituent groups selected from the group heterocycle can be further substituted with one or wherein said alkyl, alkenyl, alkynyl, polyalkyl

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P(O)R', P+R'RBA-, or phenylene. replaced by 0, NR^7 , $N^+R^7R^8A^-$, S, SO, SO₂, $S^+R^7A^-$, PR^7 heterocycle can optionally have one or more carbons polyether, aryl, haloalkyl, cycloalkyl, and wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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Exemplary core moieties include:

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wherein:

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R25 is selected from the group consisting of C and

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Further preferred compounds of the present

$$(R^{X})_{\mathbf{q}}$$

$$(0)_{\mathbf{n}}$$

$$(0)_{\mathbf{R}}$$

$$(0)_{\mathbf{R}}$$

$$(0)_{\mathbf{R}}$$

(Formula DIV)

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morpholinium, I' 9-(N)-N'-methylpiperazine 9-(N)-N'-dimethylpiperazinium,

9-(N)-pyrrolidine 9-(N)-N-methyl-pyrrolidinium, I' 9-(N)-N-methyl-

7-0CH₃, 8-0CH₃ 7-8CH₃, 8-0CH₃ 7-8CH₃, 8-8CH₃ 6-0CH₃, 7-0CH₃, 8-0CH₃

9-NH-CB2 9-NHC(0)C₅H₁₁ 9-NHC(0)CH₂Br 9-NH-C(NH)NH₂ 9-(2)-thiophene

(Formula DIVA)

as defined above, and R's is either a covalent bond or where R', R', R', R', R', R', R', X', q and n are arylene.

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The core moiety can comprise alkane diyl, alkene polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, alkyne diyl, polyalkane diyl, alkoxy diyl,

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invention comprise a core structure having two or more described above, covalently bonded to the core moiety pharmaceutically active benzothiepine structures as via functional linkages. Such active benzothiepine structures preferably comprise:

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9-N'Me)_CH_CO_H, I 9-(N)-morpholine 9-(N)-azetidine 9-(N)-N-methylazetidinium,

9-N+C(-0)CH₃), I' 9-N+C(-0)CH₃ 9-N+C(-0)CH₃ 9-N+CCH₂CO₂H

SO₂CH₃ SCH₂CH₃

-NHOH -NHCH,

or:

Table 1A: Alternative R Groups

$$(R^{x})q \xrightarrow{\prod_{i=1}^{8} g} (R^{x}) \xrightarrow{R^{2}} (R^{x}) \xrightarrow{R^{2}} (R^{x}) \xrightarrow{R^{3}} (R^{x}) ($$

```
R1, R2

R2hy]

R-propyl

n-butyl

n-pentyl

n-hexyl

iso-propyl
iso-propyl
iso-butyl
CH3C(-0)C3H3
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    CH<sub>2</sub>CH (OH) C<sub>2</sub>H<sub>5</sub>
CH<sub>2</sub>O- (4-picoline)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               - B.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          I', p-(CH<sub>3</sub>)<sub>3</sub>-N'-Ph-
I', m-(CH<sub>3</sub>)<sub>3</sub>-N'-Ph-
I', p-(CH<sub>3</sub>)<sub>3</sub>-N'-CH<sub>3</sub>CH<sub>3</sub>-
(CCH<sub>3</sub>CH<sub>3</sub>)<sub>3</sub>-O-Ph-
(CCH<sub>3</sub>CH<sub>3</sub>)<sub>3</sub>-O-Ph-
(CCH<sub>3</sub>CH<sub>3</sub>)<sub>3</sub>-O-Ph-
(CCH<sub>3</sub>CH<sub>3</sub>)<sub>3</sub>-O-Ph-
(CCH<sub>3</sub>CH<sub>3</sub>)<sub>3</sub>-O-Ph-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                p-CH<sub>3</sub>O-Ph-
p-CH<sub>3</sub>O-Ph-
m-CH<sub>3</sub>O-Ph-
p-(CH<sub>3</sub>)<sub>2</sub>N-Ph-
m-(CH<sub>3</sub>)<sub>2</sub>N-Ph-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  I', m-(N,N-dimethylpiperazine)-
(N')-CH<sub>2</sub>-(OCH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>-O-
                                                                                                                                                                                                                                               Cl-thienyl-2-yl
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  P, p-CH<sub>3</sub>O-Ph-
l,dioxymethylene-Ph
CH<sub>3</sub>O-, p-F-Ph-
                                                                                                                                                                                                                                                                                                                                     hyl-4-pyridinium, I - pyrrolidinium, I - ridine pyrrolidinium, I - pyr
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             imethylpiperazine) - N') - CH<sub>3</sub> - (OCH<sub>3</sub>CH<sub>2</sub>)<sub>2</sub>-O-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         7-N°(Ne) 2CH2CO2H, I'
7-(N)-morpholine
7-(N)-arctidine
7-(N)-N-methylazetidinium,
7-NH-CBZ
7-NHC(0) C<sub>5</sub>H<sub>11</sub>
7-NHC(0) CH<sub>5</sub>Br
7-NH-C(NH) NH<sub>5</sub>
7-(2)-thiophene
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   7-N*(CH<sub>2</sub>)<sub>3</sub>, I
7-NHC(=0) CH<sub>3</sub>
7-N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>
7-NMeCH<sub>2</sub>OO<sub>2</sub>H
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  7-(N)-pyrrolidine .
7-(N)-N-methyl-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         7-SCH<sub>2</sub>CH<sub>3</sub>
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             -iso-propyl
                                                                                                                                                                                                                                                                                                                               dimethylpiperazinium,
```

continued next page...

pyrrolidinium, I.
8-(N)-N-methyl.
Bright Marry Company 8-N*(CH₃), I*
8-NHC(4-0)CH₃
8-NHCCH₃CO₃H
8-NHCCH₃CO₃H, I*
8-N*(Ne)₃CH₃CO₃H, I*
8-(N)-averidine
8-(N)-averidine
8-(N)-averidine 8-NH-CBZ 8-NHC(0) CgH11 8-NHC(0) CH2Br 8-NH-C(NH) NH2 8-(2) -thiophene 8-SO₂CH₃ 8-SCH₂CH₃ 8-NH₃ 8-NHCH 8-(N)-pyrrolidine 8-(N)-N-methyl-9-N(CH₃)2 -SCH₃ dimethylpiperazinium,

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continued next page...

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ring via poly(oxyalkylene) linkages, e.g., - $(OCH_2CH_2)_{\kappa}$ peptide, and quaternary ammonium salts linked to the carbohydrate (e.g., a 5 or 6 carbon monosaccharide), other substituents can be advantageously present on the 6, 7, 8, and/or 9- positions of the benzo ring, including, for example, guanidinyl, cycloalkyl, N'R11R14R15A', where x is 2 to 10.

Imidazole, pyrazole, or furan. The aryl group of \mathbb{R}^5 or N,N-dialkylamino, quaternary ammonium salts, a C, to C, substituted at the p-position, the m-position, or both nexylenetrimethylammonium, tri (oxyethylene) iodide, and which the substituent(s) are selected from among halo, In further compounds of the present invention, \mathbb{R}^5 N-alkylpiperazinium, N-alkylmorpholinium, or furan in chloride counterion), methoxycarbonyl, ethoxycarbonyl dioxyalkylene, -{0(CH2,), X where x is 2 to 12, w is 2 substituted thereon, alkoxycarbonyl, aryloxycarbonyl, s' is preferably phenyl, phenylene, or benzene triyl, and R' are independently selected from among hydrogen cormyl, acetyl, propancyl, (N)-hexyldimethylammonium, substituted. Among the species which may constitute hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, pyrazole, pyrimidine, morpholine, N-alkylpyridinium, i.e., may be unsubstituted, mono-substituted, or dior 3 and X comprises halo or a quaternary ammonium fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, and ring-carbon substituted or unsubstituted aryl, thiophene, pyridine, pyrrole, thiazole, imidazole, of the aryl ring. Other substituents that can be alkylene bridge having a quaternary ammonium salt tetra (oxyethylene) trimethyl-ammonium iodide, each the substituents on the aryl ring of R or R are rrimethylammonium (preferably with an iodide or salt, thiophene, pyridine, pyrrole, thiazole, alkylcarbonyloxy and arylcarbonyloxy, (0,0)-

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properties are those in which R' or R' is selected from N'-phenyl, I m- (CH₃),-N'-CH₃CH₃- (OCH₃CH₃),-O-phenyl, I pring) and 3,4-dioxyethylene (6- membered ring). Among dimethylaminophenyl, I p-(CH,),-N'-phenyl, I m-(CH,),iluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3aromatic ring include 3,4-dioxymethylene (5-membered dimethylpiperazinium) - (N') - CH, - (OCH, CH,), - O-phenyl, 3dimethylpiperazinium) - (N') - CH₂- (OCH₂CH₃), -O-phenyl, 3compounds which have been or can be demonstrated to have desirable ileal bile acid transport inhibiting cholorothienyl-2-yl, 3,4-difluorophenyl, I p-(N,Nmethoxyphenyl, p-N,N-dimethylaminophenyl, m-N,Nlydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, pyridinyl, N-methyl-4-pyridinium, I' N-methyl-3present on a phenylene, benzene triyl or other (CH₃),-N*-CH₂CH₂- (OCH₃CH₃),-O-phenyl, I m- (N, Npyridinium, 3,4-dloxymethylenephenyl, 3,4phenyl, p-fluorophenyl, m-fluorophenyl, pmethoxy-4-fluorophenyl, thienyl-2-yl, 5ß

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preferred R'substituents in combination with the R* substituents shown in Table 1. It is particularly Preferred compounds include 3-ethyl-3-butyl and 3dioxyethylenephenyl, and p-methoxycarbonylphenyl. butyl-3-butyl compounds having each of the above preferred that one but not both of R' and R' is nydrogen.

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orientation relative to the plane of the molecule as R³ the plane of the molecule, i.e., both in $\alpha\text{-}$ or both in 8-configuration. It is further preferred that, where hydrogen, that "R' and R' not be hydrogen, and that R' and R5 be oriented in the same direction relative to It is especially preferred that R' and R' be R2 is butyl and R1 is ethyl, then R1 has the same and R5.

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Set forth in Table 1A are lists of illustrative species of R1/R2, R5/R6 and R2.

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the complementary enantiomer or set of diastereomers. Enantiomeric enrichment of a mixture of enantiomers is calculated by dividing the concentration of the preponderating enantiomer by the concentration of the other enantiomer, multiplying the dividend by 100, and expressing the result as a percent. Enantiomeric enrichment can be from about 1% to about 100%, and more preferably from about 10% to about 100%, and more preferably from about 20% to 100%.

of the compound used as an ileal bile acid transport R' are identical, for example n-butyl/n-butyl, so that and unsubstituted C1 to C10 alkyl wherein the selection, synthesis, separation, and quality control optical isomerism at the 3-carbon simplifies the the compound is achiral at the 3-carbon. Eliminating compounds of the present invention, substituents R and are preferred. In certain particularly preferred carbon can include ethyl, n-propyl, n-butyl, n-pentyl through an ether linkage. Substituents at the 3containing heterocycles joined to the C1 to C10 alkyl alkylcarbonyl, alkoxy, hydroxy, and nitrogensubstituent(s) can be selected from among (4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl isobutyl, isopropyl, -CH₂C(=0)C₂H₃, -CH₂OC₂H₃, and -CH₂O-R1 and R2 can be selected from among substituted

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In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R*) on the benzo- ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxy-carbonylalkyl amine, haloalkylthio, haloalkylsulfinyl, haloalkylsufonyl, amino, N-alkylamino, N,N-dialkylamino, (N)-alkoxycarbamoyl, (N)-aralkyloxycarbamoyl,

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υ 30 25 20 15 10 ഗ N-hexylamino, thiophene, -N'(CH₁)2CO₂H I', -NCH₂CO₂H, example the 6,7,8-trimethoxy compounds. A variety of disubstituted at the 7- and -8 positions. Also can be mono-substituted at the 6, 7 or 8 position, or methylpyrrolidinium, and -(OCH2CH3),I, where A is a butyloxycarbamoyl, (N)-methylsulfonamido, (N)N'carboxyethylamino, (N)-morpholinyl, (N)-azetidinyl, substituted thereon, - $\{0(CH_2)_v\}_{x}$ -X where x is 2 to 12, included are the 6,7,8-trialkoxy compounds, for pharmaceutically acceptable anion. The benzo ring is -(N)-N'-dimethylpiperazinium I', (N)-tand N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)dimethylamino, N,N-diethylamino, ethylthio, amino, hydroxylamine, N-methylamino, N,Nhydroxy, methoxy, ethoxy, isopropoxy, methylthio, constitute R* are methyl, ethyl, isopropyl, t-butyl, quaternized. Among the preferred species which may the nitrogen of said heterocycle is optionally salt, and (N)-nitrogen containing heterocycle wherein w is 2 or 3 and X is a halo or a quaternary ammonium an alkylene bridge having a quaternary ammonium salt substituent on one or more of the alkyl substituents, trialkylammonium salt, (N)-carbamic acid, alkyl or (N)-N-methylpyridinium A, (N)-N-methylmorpholinium A, (N)-N-methylazetidinium A', (N)-pyrrolidinyl, pyrrolyl, -NHC (=0) CH₁, -NHC (=0) C₅H₁₁, -NHC (=0) C₆H₁₁, (N)-benzyloxycarbamoyl, trimethylammonium, A iodo; bromo, fluoro, methylsulfinyl, methylsulfonyl haloacylamine, carbohydrate, thiophene a trialkyl sulfonamido, (N)-alkylsulfonamido, (N)counterion), (N)-amido, (N)-alkylamido, -N-alkylamido, ammonium salt having a carboxylic acid or hydroxy benzyl ester, N-acylamine, hydroxylamine, haloalkylsulfonamido, carboxyalkyl-amino, -N,N-dialkylamido, (N)-haloalkylamido, trialkylammonium (especially with a halide

$$\begin{array}{c|c}
S & R' \\
S & R^{\parallel} \\
W_{1}R^{2} \\
OH & Hg(OTf)_{2} \\
\hline
VXX & Pd catalvst
\end{array}$$

Abbreviations used in the foregoing description have the following meanings:

THF---tetrahydrofuran

PTC---phase transfer catalyst

Aliquart 336 -- - methyltricaprylylammonium chloride

Celite--- a brand of diatomaceous earth filtering MCPBA --- m-chloroperbenzoic acid

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DMF---dimethylformamide

DME----ethylene glycol dimethyl ether

BOC---t-butoxycarbonyl group

Me - - '- methyl

Et---ethyl Bu---butyl

EtOAc---ethyl acetate

CH2Cl2---methylene chloride

Et,0---diethyl ether

MgSO. --- magnesium sulfate

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NaOH---sodium hydroxide CH,OH---methanol

HCl --- hydrochloric acid

NaCl --- sodium chloride

NaH -- - sodium hydride

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LAH --- lithium aluminum hydride

LiOH---lithium hydroxide

Na,SO, --- sodium sulfite

NaHCO, --- sodium bicarbonate

DMSO---dimethylgulfoxide

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KOSiMe, --- potassium trimethylsilanolate PEG---polyethylene glycol

MS---mass spectrometry

HRMS---high resolution mass spectrometry

NMR---nuclear magnetic resonance spectroscopy ES---electrospray

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GC---gas chromatography

MPLC---medium pressure liquid chromatography HPLC---high pressure liquid chromatography

RPHPLC -- reverse phase high pressure liquid

chromatography

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RT---room temperature

h or hr---hour(s)

min---minute(s)

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"Enantiomerically-enriched" (e.e.) means that one enantiomer or set of diastereomers preponderates over

XXV with hydrogen followed by reductive alkylation of the resulting amino derivative with hydrogen and an aldehyde catalyzed by palladium on carbon in the same reaction vessel yields the substituted amine derivative XXVIII. Cyclization of XXVIII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention XXIXc and XXIXd.

79 Scheme 6

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Scheme 7 describes one of the methods of introducing a substituent to the aryl ring at the 5-position of benzothiepine. Iodination of 5-phenyl derivative XXX with iodine catalyzed by mercuric triflate gives the iodo derivative XXXI, which upon palladium-catalyzed carbonylation in an alcohol yields the carboxylate XXXII.

10 Hydrolysis of the carboxylate and derivatization of the resulting acid to acid derivatives are well known in the art.

hydroxylamine XXV with di-t-butyldicarbonate gives the

N, O-di-(t-butoxycarbonyl)hydroxylamino derivative

and removal of the t-butoxycarbonyl protecting group XXVI. Cyclization of XXVI with potassium t-butoxide

gives a mixture of hydroxylamino derivatives XXVIIc and XXVIId. The primary amine XXXIIIc and XXXIIId

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derivatives can also be prepared by further hydrogenation of XXIV or XXVIIc and XXVIId.

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Pd/C-H₂ 100 psi 50 deg C

1. potassium t-butoxide XXX 2. acid workup

In Scheme 6, reduction of the sulfone-aldehyde

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Scheme 2

a mixture of benzothiepine XXII sulfide-aldehyde with potassium t-butoxide also gives butoxide to a mixture of Xc and Xd. Cyclyzation of to give the sulfide-aldehyde XXI. Oxidation of XXI 1,1-dioxides XC and Xd starting from the thiophenol aldehyde XIV which can be cyclized with potassium twith two equivalents of MCPBA yields the sulfone-XVIII. Compound XVIII can be reacted with mesylate IV Scheme 4 shows another route to benzothiepine.

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$$(R^{1})_{q}^{Q} \xrightarrow{\text{SH}} R^{6} + \frac{M_{SO}}{R^{7}} \frac{R^{1}}{R^{8}} \frac{R^{2}}{H^{0}} \xrightarrow{\text{NVIII}} N$$

Oxidation of XXIII with 2 equivalents of MCPBA yields hydrogenation to the hydroxylamine XXV. Protecting the sulfone-aldehyde XXIV which can be reduced by sulfide followed by reacting the resulting sulfide nitrobenzophenone is reduced with triethylsilane and compounds of the present invention can be prepared as with mesylate IV gives sulfide-aldehyde XXIII. nitrodiphenylmethane 32. Reaction of 32 with lithium trifluoromethane sulfonic acid to 2-chloro-4shown in Scheme 5 and Scheme 6. 2-Chloro-4-Examples of amine- and hydroxylamine-containing

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HOR, or HNRR', or

 $R^5 = OR$, NRR', S(O)_nR

HS(O),R IX, where R5 = H Another route to Xc and Xd of the present invention is chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture shown in Scheme 2. Compound VI is oxidized to of Xc and Xd. Separation of Xc and Xd can be accomplished by either HPLC or fractional compound XIII with two equivalent of mcrystallization.

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invention can also be prepared according to the Scheme procedure in J. Chem. Soc., 2431-2432 (1958) gives the ortho substituted phenol XVI. The phenol XVI can be The thiophenols XVIII and V used in the present chloride in a nonpolar solvent according to the 3. Alkylation of phenol XV with an arylmethyl converted to the thiophenol XVIII via the

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thermally rearranged at 200-300 °C, and the rearranged product is hydrolyzed with sodium hydroxide to yield org. Chem., 31, 3980 (1966). The phenol XVI is first chiocarbamate XVII by the procedure described in J. riethylamine to give thiocarbamate XVII which is reacted with dimethyl thiocarbamoyl chloride and

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when R1= butyl, R2=ethyl, R5=phenyl, X=H, q = 4

qx = q96c = Xc 6a = Xa

pX = p9

MCPBA = m-chloroperbenzoic acid

PTC = phase transfer catalyst

the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate

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thiocarbamate XX.

The compounds of the present invention where R' is OR, NRR' and S(O),R and R' is hydroxy can be prepared by reaction of epoxide IX where R' is H with thiol, alcohol, and amine in the presence of a base.

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prepared by reaction of thiophenol V with a 2substituted acrolein. Alternatively, keto-aldehyde VI where R^2 is H can be

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also be carried out with potassium t-butoxide in THF. phase transfer catalyst (PTC). The transformation can with 40-50% sodium hydroxide in the presence of a give four racemic stereoisomers of X. The two XII which can be reduced with sodium borohydride to MCPBA to give the benzothiepin-(5H)-4-one-1,1-dioxide benzothiepine ring by reaction in methylene chloride having the OH group and R' on the same side of the be converted to the other two isomers of X, Xc and Xd, R' on the opposite sides of the benzothiepine ring can stereoisomers of X, Xa and Xb, having the OH group and Benzothiepin-(5H)-4-one VIII can be oxidized with

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of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

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Compounds

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The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

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Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the compounds of the present invention.

The compounds of the present invention also include tautomers.

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The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

Compound Syntheses

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The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

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Generally, the compounds of the present invention can be prepared by the procedures described below.

For example, as shown in Scheme I, reaction of aldehyde II with formaldehyde and sodium hydroxide

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nydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X give a mixture of 2,3-dihydrobenzothiepine VII and two when R' and R' are nonequivalent. Oxidation of VII with Chem. Ber. 98, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described yields keto-aldehyde VI which can be cyclized with the hydrogenation with palladium on carbon as the catalyst in refluxing ethylene glycol dimethyl ether (DME), to reagent, prepared from zinc and titanium trichloride yields the hydroxyaldehyde III which is converted to racemic steroisomers of benzothiepin- (5H) -4-one VIII and two racemic stereoisomers of 2,3,4,5-tetrahydrotriethylamine similar to the procedure described in yield a mixture of four racemic stereoisomers of 4-3 equivalents of m-chloro-perbenzoic acid (MCPBA) in WO 93/16055, in the presence of triethylamine penzothiepine-1,1-dioxides XI when R' and R' are gives isomeric sulfone-epoxides IX which upon mesylate IV with methansulfonyl chloride and nonequivalent.

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Optically active compounds of the present invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in J. Org. Chem., 39, 3904 (1974), ibid., 42, 2781 (1977), and ibid., 44, 4891 (1979).

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one or more heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

heteroaryl groups attached to an alkyl radical having groups. Preferable heteroarylalkyl radicals are "lower one to ten carbon atoms. that is substituted with one or more heteroaryl heteroarylalkyl" radicals having one or more The term "heteroarylalkyl" means an alkyl radical

alkyl radical that is substituted .with one or more radical having one to ten carbon atoms. quaternary heterocycle groups attached to an alkyl heterocyclylalkyl" radicals having one or more heterocyclylalkyl radicals are "lower quaternary quaternary heterocycle groups. Preferable quaternary The term "quaternary heterocyclylalkyl" means an

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quaternary heteroaryl groups. Preferable quaternary radical having one to ten carbon atoms. quaternary heteroaryl groups attached to an alkyl heteroarylalkyl" radicals having one or more heteroarylalkyl radicals are "lower quaternary alkyl radical that is substituted with one or more The term "quaternary heteroarylalkyl" means an

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or more alkyl groups. Preferable alkylheteroarylalkyl with alkyl portions having one to ten carbon atoms. heteroarylalkyl radical that is substituted with one radicals are "lower alkylheteroarylalkyl" radicals The term "alkylheteroarylalkyl" means a

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carbon atoms. Examples of such radicals include such as a methoxy radical. More preferred alkoxy attached to the remainder of the molecule by oxygen, methoxy, ethoxy, propoxy, iso-propoxy, butoxy and radicals are "lower alkoxy" radicals having one to six tert-butoxy. The term "alkoxy" an alkyl radical which is

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유 its salts. The term "carboxy" means the carboxy group, -CO2H,

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carbon atoms. groups attached to an alkyl radical having one to six carboxyalkyl" radicals having one or more carboxy Preferable carboxyalkyl radicals are "lower that is substituted with one or more carboxy groups. The term "carboxyalkyl" means an alkyl radical

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radical that is substituted with one or more carboxy The term "carboxyheterocycle" means a heterocycle

groups. radical that is substituted with one or more carboxy The term "carboxyheteroaryl" means a heteroaryl

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alkoxycarbonyl groups. Preferable carboalkoxyalkyl radical having one to six carbon atoms. radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical that is substituted with one or more The term "carboalkoxyalkyl" means an alkyl

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20 the carboxy group is attached to an alkyl radical substituent is a "lower carboxyalkyl" radical wherein radical that is mono- or di-substituted with carboxyalkyl. Preferably, the carboxyalkyl having one to six carbon atoms. The term "carboxyalkylamino" means an amino

25 the present invention which inhibits transport of bile The term "active compound" means a compound of

listed above have the meaning indicated above. "alkylaryl" or "arylalkyl," the individual terms When used in combination, for example

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as reducing the blood plasma or serum concentrations increasing the fecal excretion of bile acids, as well of a mammal, such as a human. a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system The term "a bile acid transport inhibitor" means This includes

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The term " halogen" means a fluoro, chloro, bromo or iodo group.

The term " haloalkyl" means alkyl substituted with one or more halogens.

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The term "cycloalkyl" means a mono- or multiringed carbocycle wherein each ring contains three to ten carbon atoms, and wherein any ring can contain one or more double or triple bonds. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepine.

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The term "diyl" means a diradical moiety wherein said moiety has two points of attachment to molecules of interest.

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The term "oxo" means a doubly bonded oxygen.

The term "polyalkyl" means a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000,

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The term "polyether" means a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

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The term "polyalkoxy" means a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

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The term "cycloalkylidene" means a mono- or multi-ringed carbocycle wherein a carbon within the ring structure is doubly bonded to an atom which is not within the ring structures.

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The term "carbohydrate" means a mono-, di-, tri-, or polysaccharide wherein the polysaccharide can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan.

The term "peptide" means polyamino acid containing up to about 100 amino acid units.

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The term "polypeptide" means polyamino acid containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid units, most preferably from about 100 amino acid units to about 500 amino acid units.

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The term " alkylammoniumalkyl" means a NH, group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is

bonded to the molecule of interest.

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The term " triazolyl" includes all positional isomers. In all other heterocycles and heteroaryls which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocycles and heteroaryls.

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The term "sulfo" means a sulfo group, - SO_3H , or its salts.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

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The term "arylalkyl" means an aryl-substituted alkyl radical such as benzyl. The term "alkylarylalkyl" means an arylalkyl radical that is substituted on the aryl group with one or more alkyl groups.

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The term "heterocyclylalkyl" means an alkyl radical that is substituted with one or more heterocycle groups. Preferable heterocyclylalkyl radicals are "lower heterocyclylalkyl" radicals having

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description.

DETAILED DESCRIPTION OF THE INVENTION

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scope of the present inventive discovery. skill in the art without departing from the spirit or discussed herein can be made by those of ordinary as modifications and variations in the emobodiments not be construed to unduly limit the present invention aid those skilled in the art in practicing the present invention. Even so, this detailed description should The following detailed description is provided to

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within these primary references, are herein herein, including the contents of the references cited incorporated by reference in their entirety. The contents of each of the references cited

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Definitions

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definitions are provided following detailed description, the following In order to aid the reader in understanding the

and ethynyl, propynyl, butynyl, pentynyl, or hexynyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl example, methyl, ethyl, propyl, butyl, pentyl or hexyl respectively and isomers thereof. in the present invention and therefore mean, for alkyl or two to twenty carbons for alkenyl and alkynyl chain hydrocarbons of from one to twenty carbons for otherwise noted are each straight chain or branched "Alkyl", "alkenyl," and "alkynyl" unless

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ring carbocyle, including, but not limited to, anthracenyl. substituted or unsubstituted phenyl, naphthyl, or "Aryl" means a fully unsaturated mono- or multi-

"Heterocycle" means a saturated or unsaturated

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carbon atoms can be replaced by N, S, P, or O. mono- or multi-ring carbocycle wherein one or more includes, for example, the following structures:

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Z" or Z" ' only when each is C. substituents are understood to be attached to Z, Z', another 0 or S atom. Furthermore, the optional another Z atom by a double bond or when attached to than carbon, but is not 0 or S when attached to the proviso that one of Z, Z', Z" or Z" ' is other wherein Z, Z', Z" or Z"' is C, S, P, O, or N, with

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heterocycle. The term "heteroaryl" means a fully unsaturated

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at the heteroatom or elsewhere within the ring. point of attachment to the molecule of interest can be In either "heterocycle" or "heteroaryl," the

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elsewhere. molecule of interest can be at a heteroatom or attachment of the quaternary heterocycle to the that it is positively charged. The point of for example, O, N, S, or P, has such a number of bonds heterocycle in which one or more of the heteroatoms, The term " quaternary heterocycle" means a

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molecule of interest can be at a heteroatom or attachment of the quaternary heteryaryl to the that it is positively charged. The point of for example, 0, N, S, or P, has such a number of bonds heteroaryl in which one or more of the heteroatoms, The term "quaternary heteroaryl" means a

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In another aspect, the present invention provides treatment of a disease or condition for which a bile a pharmaceutical composition for the prophylaxis or

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atherosclerosis. Such compositions may comprise any pharmaceutically acceptable carrier, excipient, or combination, in an amount effective to reduce bile thereof across digestive system membranes, and a acid transport inhibitor is indicated, such as a acid levels in the blood, or to reduce transport of the compounds disclosed above, alone or in hyperlipidemic condition, for example, diluent.

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compounds disclosed above, alone or in combination, in an effective amount in unit dosage form or in divided In a further aspect, the present invention also provides a method of treating a disease or condition in mammals, including humans, for which a bile acid administering to a patient in need any of the transport inhibitor is indicated, comprising

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above, alone or in combination, in the preparation of In a further aspect, the present invention also condition in mammals, including humans, for which a provides the use of any of the compounds disclosed a medicament for use in treating a disease or bile acid transport inhibitor is indicated.

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and

In yet a further aspect, the present invention compounds of the present invention as discussed in also provides processes for the preparation of greater detail below.

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understood that the following detailed description and spirit and scope of the invention will become apparent Further scope of the applicability of the present the invention, are given by way of illustration only examples, while indicating preferred embodiments of since various changes and modifications within the description provided below. However, it should be invention will become apparent from the detailed to those skilled in the art from this detailed

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and

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discussed immediately above, benzothiepine compounds In any of the dimeric or multimeric structures of the present invention can be used alone or in various combinations.

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In any of the compounds of the present invention, R¹ and R² can be ethyl/butyl or butyl/butyl.

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Another class of compounds of interest includes the following compounds:

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S'R"R"A', and N'R9R11R12A-; C(0)OM, COR^{13} , $P(0)R^{13}R^{14}$, $P^{+}R^{13}R^{14}R15A^{-}$, $P(OR^{11})OR^{14}$ NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(0)\text{NR}^{13}\text{R}^{14}$,

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R3 comprises a benzothiepine moiety as described above compounds of Formula DIII. Each of R20, R21, or R22 and bile acid transport. that is therapeutically effective in inhibiting ileal by which R19 is bonded to R20, R21, or R22 in the compounds of Formulae DII and DIII, and \mathbb{R}^{23} in the wherein R's further comprises functional linkages

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comprises a benzothiepine moiety corresponding to the Formula DIII in which each of R20, R21, R22 and R23 selected from among Formula DI, Formula DII and The invention is also directed to a compound

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(Formula DIV)

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(Formula DIVA)

either a covalent bond or arylene. as defined in Formula I as described above, and R is wherein R', R', R', R', R', R', R', R", q, and n are

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moiety bonded at a m- or p-carbon thereof to R1. is particularly preferred that R's comprise a phenylene or 8-position to R19. In compounds of Formula DIVA, it and DIII, and R21 in Formula DIII, be bonded at its 7preferred that each of R20, R21, and R22 in Formulae DII In compounds of Formula DIV, it is particularly

Examples of Formula DI include:

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$$\begin{bmatrix} O \xrightarrow{R^0} R^1 & R^2 & R^{10} & R^{10$$

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are n-butyl; and/or

(2) R' and R' are independently selected from the group consisting of hydrogen and OR' wherein R' is defined as set forth above. Preferably, R' is hydrogen and R' is OR'. Still more preferably, R' is hydrogen and R' is hydroxy; and/or

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substituted aryl. Preferably, R⁵ is phenyl substituted phenyl. More preferably, R⁵ is phenyl substituted with a radical selected from the group consisting of OR¹¹, NR¹²C(O)R¹⁴, NR¹³C(O)R¹⁴, NR¹³CO₁R¹⁴, NR¹⁴CO₁R¹⁵, R¹⁵ is phenyl substituted with OR¹³. Still more preferably, R⁵ is phenyl substituted at the para or meta position with OR¹³ wherein R¹³ comprises a quaternary heterocycle, quaternary heterocycle,

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R' is hydrogen; and/or

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(5) R' and R' are independently selected from the group consisting of hydrogen and alkyl. Preferably, R' and R' are independently selected from the group consisting of hydrogen and C_{1.4} alkyl. Still more preferably, R' and R' are hydrogen; and/or

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(6) \mathbb{R}^{x} is selected from the group consisting of OR^{13}

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and NR¹³K¹⁴. Preferably, R² is selected from the group consisting of alkoxy, amino, alkylamino and dialkylamino. Still more preferably, R² is selected from the group consisting of methoxy and dimethylamino.

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The invention is further directed to a compound selected from among:

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and

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wherein R¹⁹ is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide, wherein alkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can optionally have one or more carbon atoms replaced by O, NR⁷, N⁺R⁷R⁸, S, SO, SO₂, S⁺R⁷R⁸, PR⁷R⁸, phenylene, heterocycle, quatarnary heterocycle, quaternary heterocycle, aryl,

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wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl,

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(dimethylamino) - tetrahydrobenzothiepine-1,1-dioxide which is then demethylated to form the intermediate 5-(3'-hydroxyphenyl)-7-

(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the 5-(3'-methoxyphenyl)-7-(dimethylamino)-

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tetrahydrobenzothiepine-1,1-dioxide preferably is subjected to a chiral chromatagraphic purification step prior to demethylation. The separated enantiomer is then demethylated to yield the enantiomeric-enriched intermediate 5-(3'-hydroxyphenyl)-7-(dimethylamino)-tetrahydrobenzothiepine-1,1-dioxide for use in the next step of the synthesis. By way of further illustration, chiral chromatographic purification could be performed immediately prior to Step 9 of Example 1400 with the separated enantiomer then used as the intermediate in Step 9 of the synthesis thereby resulting in an enantiomeric-enriched final product.

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Further, chiral chromatographic purification can be used where the synthesis proceeds through the intermediate 5-(3' or 4'-aminophenyl)-7- (dimethylamino) tetrahydro-benzothiepine-1,1-dioxide, such as in the Example Corresponding To Scheme XII. For example, chiral chromatographic purification could be performed immediately following Step 5 of the Example Corresponding To Scheme XII to yield the enantiomericenriched intermediate 5-(3' or 4-aminophenyl)-7- (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide for use in the next step of the synthesis.

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Alternatively, an enantioselective synthesis, such as the one described in Example 1461 below, could be used to provide the desired enantiomeric-enriched 5-(3' or 4'-aminophenyl)-7-

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(dimethylamino) tetrahydrobenzothiepine-1,1-dioxide

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Preparation of:

Step 1: Preparation of triflic intermediate

A solution of 10.17 g (22.13 mmol) of 5-(4'-hydroxyphenyl)-7-

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the desired title compound as a pale yellow foam (11.42 evaporated. The residue was purified by chromatography nl) at 0°C under nitrogen gas was treated with triflic vacuo, the resulting oil was taken up in water (100 mL) temperature for 21 hours. The pyridine was removed in(m, 10H), 1.76 (t, J = 12.6 Hz, 1 H), 2.12 (t, J = 13 Hz, 1H), 2.79 (8, 6H), 3.1-3.2 (Que, 2H), 4.05 (8, 1H), on silica gel (25% ethyl acetate in hexane) to afford 3, 87.2%): ¹H NMR (CD₃OD) & 0.85-1.0 (m, 6H), 1.0-1.15 prepared in Step 7 of Example 1398a) in pyridine (42 dropwise. Upon completion of the addition, the bath each). The combined organics were washed with 2N HCl (100 mL), 10% CuSO, (100 mL) and brine (100 mL), and and extracted three times with ethyl acetate (45 mL (dimethylamino) tetrahydrobenzothiepine-1,1-dioxide then dried over MgSO,, filtered and the solvent anhydride (4.1 mL, 24.4 mmol, 1.1 equivalents) was removed and the reaction atirred at room

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8.9, 2.1 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (d, J

5.42 (8, 1H), 5.88 (d, J = 2.1 Hz, 1H), 6.59 (dd, J =

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= 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.66 (8, 1H), 7.77 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of Imine

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7.52 (m, 7H), 7.52-7.68 (m, 2H), 7.71 (d, J = 7.9 Hz, J = 9.1, 2.7 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.806.6 mL (39.4 mmol, 2.0 equivalents) of benzophenone 2.0 equivalents) in 114 mL of tetrahydrofuran was added mmol, 12 mol%) and cesium carbonate (8.86 g, 27.2 mmol, acetate (433 mg, 1.93 mmol, 10 mol%), racemic 2,2'-bistriflate (prepared in Step 1 above), palladium (II) 1H), 5.17 (s, 1H), 5.92 (d, J = 2.2 Hz, 1H), 6.54 (dd hours, filtered through celite and the solvent removed imine. The mixture was stirred at reflux for four (br s, 1H), 7.0-7.12 (m, 2H), 7.15-7.25 (m, 3H), 7.35-(CDOD₃) & 0.8-1.45 (m, 16H), 1.6-1.75 (m, 1H), 1.9-2.05 in vacuo providing 19.11 g of a deep red foam: 1H NMR (biphenylphosphenyl)-1,1'-binaphthyl (1.41 g, 2.26 (m, 1 H), 2.78 (s, 6H), 2.98-3.15 (q_M, 2H), 3.88 (s, To a solution of 11.41 g (19.28 mmol) of the

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Step 3: Preparation of Aniline

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To a solution of 19.1 g (theoretically 19.3 mmol) of the crude imine (prepared in Step 2 above) in methanol (200 mL) was added sodium acctate (6.33 g, 77.2 mmol, 4 equivalents) and hydroxylamine hydrochloride (4.02 g, 57.9 mmol, 3 equivalents). After stirring one hour, 1N sodium hydroxide (100 mL) was added and the mixture extracted with methylene chloride (2 X 100 mL, 1 X 50 mL). The combined organics were washed with brine (100 mL), dried over MgSO, filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (50% ethyl acetate in hexane) to afford the desired title compound as a yellow foam (8.64 g, 97.9%): ¹H NMR

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 (CD_3OD) & 0.86-0.97 (m, 6H), 1.07-1.52 (m, 10H), 1.76 (t, J=12.6 Hz, 1 H), 2.10 (t, J=11.5 Hz, 1H), 2.79 (e, 6H), 3.05-3.18 (Q_{AM} , 2H), 4.10 (s, 1H), 5.22 (s, 1H), 6.19 (s, 1H), 6.54 (dd, J=8.9, 1.9 Hz, 1H), 6.68 (d, J=8 Hz, 1H), 6.82 (s, 1H), 6.86 (d, J=7.2 Hz, 1H), 7.14 (t, J=7.8 Hz, 1H), 7.73 (d, J=8.9 Hz, 1H)

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BIOLOGICAL ASSAYS

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The utility of the compounds of the present invention is shown by the following assays. These assays are performed in vitro and in animal models essentially using a procedure recognized to show the utility of the present invention.

In Vitro Assay of compounds that inhibit IBAT-mediated uptake of ["C]-Taurocholate (TC) in H14 Cells

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Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded at 60,000 cells/well in 96 well Top-Count tissue culture plates for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours. On the day of assay, the cell monolayer is gently

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washed once with 100 μ l assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose + 0.2% (w/v) fatty acid free bovine serum albumin- (FAF)BSA). To each well 50 μ l of a two-fold concentrate of test compound in assay buffer is added along with 50 μ l of μ ['C]-taurocholate in assay buffer (final concentration of 3 μ M ['C]-taurocholate). The cell culture plates are incubated 2 hours at 37° C prior to gently washing each well twice with 100 μ l 4° C pubecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed

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once with 100 μ l 4° C PBS without (FAF)BSA. To each 200 μ l of liquid scintillation counting fluid is added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

In Vitro Assay of compounds that inhibit uptake of

(1'C)-Alanine

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The alanine uptake assay is performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

15 In Vivo Assay of compounds that inhibit Rat Ileal

uptake of [''C]-Taurocholate into Bile

(See" Metabolism of 3α , 7β -dihydroxy- 7α -methyl- 5β -cholanoic acid and 3α , 7β -dihydroxy- 7α -methyl- 5β -cholanoic acid in hamsters" in Biochimica et Biophysica Acta 833 (1985) 196-202 by Une et al.)

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min with warm PBS at 0.25 ml/min. Temperature of the this same junction (utilizing a 8 cm length of ileum) canulae (1/8" luer lock, tapered female adapter) is intestine and the cecum. A slit is cut at 4 cm from segment. The distal opening is cannulated with a 20 gut segment is monitored continuously. At the start 20 ml of warm Dulbecco's phosphate buffered saline, peristaltic pump and the intestine is washed for 20 with inactin @100 mg/kg. Bile ducts are cannulated Male wistar rats (200-300 g) are anesthetized cm length of silicone tubing (0.02" I.D. \times 0.037" intestine is exposed and laid out on a gauze pad. Inserted at 12 cm from the junction of the small pH 6.5 (PBS) is used to flush out the intestine 0.D.). The proximal cannulae is hooked up to a with a 10" length of PE10 tubing. The small

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of the experiment, 2.0 ml of control sample (["C]-taurocholate @ 0.05 mi/ml with 5 mM cold taurocholate) is loaded into the gut segment with a 3 ml syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 ml/min for 21 min. Bile samples fractions are collected every 3 minute for the first 27 minutes of the procedure. After the 21 min of sample infusion, the ileal loop is washed out with 20 ml of warm PBS (using a 30 ml syringe), and then the loop is washed out for 21 min with warm PBS at 0.25 ml/min. A second perfusion is initiated as described above but this with test compound being administered as well (21 min administration followed by 21 min of wash out) and bile sampled every 3 min

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Measurement of Hepatic Cholesterol Concentration

for the first 27 min. If necessary, a third perfusion

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is performed as above that typically contains the

control sample.

(HEPATIC CHOL)

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Liver tissue was weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant was separated and dried under nitrogen. The residue was dissolved in isopropanol and the cholesterol content was measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., et al. (1974) Clin. Chem. 20, 470.

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30 Measurement of Hepatic HMG CoA-Reductage Activity (HMG

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for HMG CoA reductase activity by incubating for 60

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minutes at 37° C in the presence of 'C-HMG-COA (Dupont-NEN). The reaction was stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant was separated, by thin-layer chromatography, and the spot corresponding to the enzyme product was scraped off the plate, extracted and radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) J. Lipid Res. 31, 2159).

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Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)

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Total serum cholesterol (SER.CHOL) was measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) was assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) were assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations were calculated as the difference between total and HDL cholesterol.

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Measurement of Hepatic Cholesterol 7-q-Hydroxylase Activity (7a-OHase)

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Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for cholesterol 7-a-hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent was evaporated and the residue was dissolved in acetonitrile/ methanol. The enzymatic product was

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separated by injecting an aliquot of the extract onto a C₁₀ reversed phase HPLC column and quantitating the eluted material using UV detection at 240nm. (Reference: Horton, J. D., et al. (1994) J. Clin. Invest. 93, 2084).

Rat Gavage Assay

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Male Wister rats (275-300g) are administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% Tween 80 in water) is administered once a day (9:00-10:0 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight. Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described below. Compound efficacy is determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

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Measurement of Fecal Bile Acid Concentration (FBA)

hamsters was collected for 24 or 48 hours, dried under

Total fecal output from individually housed

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a stream of nitrogen, pulverized and weighed.

Approximately 0.1 gram was weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue was dissolved in methanol and the amount of bile acid present was measured enzymatically using the 3α-hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., et al. (1981) Clin. Chem. 27, 1352).

['H] taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

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Rabbit Ileal brush border membranes were prepared

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ul solution containing $2\mu M$ [^{3}H]-taurocholate(0.75 μCi), vortexing and the reaction was stopped by the addition instead of 100 μ l. Briefly, at room temperature a 190 nylon filter (0.2 μm pore) and an additional 5 ml wash Biochimica Biophysica Acta, 554, 259). The method for measuring taurocholate was essentially as described by Kramer et al. (Reference: (1992) Biochimica Biophysica mebrane vesicles (60-120 μg protein). The incubation from frozen ileal mucosa by the calcium precipitation of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM method describe by Malathi et al. (Reference: (1979) 10 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was Acta, 1111, 93) except the assay volume was 200 μ l KCl) followed immediately by filtration through a was initiated by the addition of the BBMV while ncubated for 5 sec with 10 µl of brush border with stop buffer.

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Acyl-CoA, cholesterol Acyl Transferase (ACAT)

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chloroform phase was taken to dryness and then spotted Hamster liver and rat intestinal microsomes were The assay consisted of a Reference: (1980) J. Biol. Chem. 255, 9098) and used ouffer containing 0.25 % BSA and 200 µg of microsomal oleoyl-CoA. The reaction went for 5 min at 37° C and protein. The assay was initiated by the addition of .0 ml incubation containing 24 µM Oleoyl-CoA (0.05 squeous phases of the extraction were separated by LCi) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 To the extraction was idded 125 μg of cholesterol oleate in chloroform nethanol to act as a carrier and the organic and on a silica gel 60 TLC plate and developed in centrifugation after thorough vortexing. The prepared from tissue as described previously was terminated by the addition of 8.0 ml of is a source of ACAT enzyme. chloroform/ methanol (2:1).

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hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard instaimager.

TABLE 11
Rat Gavage Assay Data for Some Additional Compounds
of the Present Invention

		Т	_			Г		_	_	Г		_		Г		_		_	_						Г	-	_	-	_	-			-		_		-
Delta	fecal bile		58.2	1.3	0.3	€.02	40.9	48.5	22.9	41.6	35.2	11.9	٣	93.7	59.1	33.5	47.8	31.6	12.8	-8.5	51.9	30.1	27.5	6.4	35	12.7	÷.04	-4.5		41.2	36.8	16.8	-3.3	26.2	45.2	26.3	9,9
	(mg/kg/day)	,	. ·	7.	. 04	2	4.	80.	.016	2	4.	80.	.016	5	.2	.04	 2	4.	80,	.016	7	4.	80.	.016	2	4.	80.	.016		7	4.	80.	.016	2	4.	80.	.016
N P	study NO.		28			30				30				28			32		•		32				33					59	•			37			
9 0 00000	Example No.		7067			1402				1403				1404			1406				1407				1407					1408				1408			

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		1418		1417		i	1416			1415		1415			1414		1414		1413				1411			1410			410			409			409		
		29		. 31			29			37		28			31		27		6	3.6		1	34			35			33			41			<u>.</u>		258
	.016	N	.016	2.4.	.016	. 0.4	2	.016) . B	N	.04	N .	.016	.08	ده ۵	.04	N U	.04	; is 1	5	.08	4.	2	.016	08	2	9.3	27.9	32.4	.016	. 80	. .	.016	.08	**		
,	-4.6 -10	20.u	29.3	0 4 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	-7.8	21.9 25	46.1	12.7	27.1	3 48.9 7 9	23.9	48.1	3.8	29	33.7	14.3	39.5	15 3	42.4	52.3	22.3	54.1	63.4	20.4		26.2				11	14.5	W # . 6	-1.7	14.1	28.7	3	

.4 .08 .016 .016 .016

37.7 41.7 40.5 24.6 54.3 51.8 26.8

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1.1	34.5	24.9	18.7	9.5	47.1	31.1	35.5	4.8	51.2	50.4	20.7	-5.6					36.2	9.7	2.4	66.5	47.4	26.5
.016	2	₹.	80.	.016	2	4.	80.	.016	2	₹.	80.	016	28.3	45.8	21.9	1.1	2	.2	\$0.	20	7	.2
	41				42				30				32				28			24		
	1429				1429				1430			_	1431				1432			1433		

The examples herein can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

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WHAT IS CLAIMED IS:

.. A compound of formula (I):

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wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylatyl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^MA⁻, SR⁹, S'R^{*}R¹⁰A⁻. p⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹, N⁺R⁹R¹⁰A.,

s, so, so₂, s⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, or phenylene,

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arylalkyl, carboxyalkyl, carboxyheteroaryl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, from the group consisting of H, alkyl, alkenyl, alkynyl carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino alkylammoniumalkyl; or heteroarylalkyl, heterocyclylalkyl, and wherein R^9 , R^{10} , and R^W are independently selected

they are attached form C3-C10 cycloalkyl; ${ t R}^1$ and ${ t R}^2$ taken together with the carbon to which

wherein R' and R' are as defined above; or heterocycle, cR^9 , vR^9R^{10} , sR^9 , $s(0)R^9$, so_2R^9 , and so_3R^9 consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl ${ t R}^3$ and ${ t R}^4$ are independently selected from the group

NR9, or CR11R12, ${
m R}^3$ and ${
m R}^4$ together form =0, =NOR 11 , =5, =NNR $^{11}{
m R}^{12}$

OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, defined above, provided that both ${\ensuremath{\text{R}}}^3$ and ${\ensuremath{\text{R}}}^4$ cannot be OH the group consisting of H, alkyl, alkenyl, alkynyl, aryl, NH, and SH, or halogen, oxo, and $\mathtt{CONR}^9\mathtt{R}^{10}$, wherein \mathtt{R}^9 and \mathtt{R}^{10} are as wherein R^{11} and R^{12} are independently selected from

atom to which they are attached form a cyclic ring; ${\mathbf R}^{11}$ and ${\mathbf R}^{12}$ together with the nitrogen or carbon

 ${\tt R}^{\tt S}$ is aryl substituted with one or more ${\tt OR}^{\tt 13a}$

alkylheterocyclylalkyl, heterocyclylalkyl, of alkylarylalkyl, alkylheteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl heteroarylalkyl, quaternary heterocyclylalkyl, wherein R^{13a} is selected from the group consisting

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 $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $S0_{2}R^{9}$, $S0_{3}R^{9}$, OXO, $CO_{2}R^{9}$, CNgroups selected from the group consisting of hydroxy, $_{P}^{+}R^{9}R^{10}R^{11}A^{-}$, $_{S}^{+}R^{9}R^{10}A^{-}$, and $_{C}(0)OM$, halogen, $\operatorname{CONR}^9 \operatorname{R}^{10}$, $\operatorname{SO}_2 \operatorname{OM}$, $\operatorname{SO}_2 \operatorname{NR}^9 \operatorname{R}^{10}$, $\operatorname{PO}(\operatorname{OR}^{16}) \operatorname{OR}^{17}$, quaternary heteroarylalkyl, guanidinyl, OR⁹, NR⁹R¹⁰ quaternary heteroaryl, quaternary heterocyclylalkyl, heteroaryl, sulfoalkyl, quaternary heterocycle, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, \mathbb{R}^{13a} is optionally substituted with one or more

and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable anion

the substituents constituting R^9 and M; and wherein R^{16} and R^{17} are independently selected from

quaternary heterocycle, OR³⁰, SR⁹, S(0)R⁹, SO₂R⁹, and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, R^6 is selected from the group consisting of H,

NR13502R14, NR1350NR14R15, NR13502NR14R15, P(0)R13R14, NR11C(0)NR14R15, NR11CO2R14, OC(0)R11, OC(0)NR13R14, NR11SOR14, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13} , $NR^{13}C(O)R^{14}$ SO3R13, NR13OR14, NR13NR14R15, NO2, CO2R13, CN, OM. halogen, oxo, OR 13 , NR 13 R 14 , SR 13 , S(O)R 13 , SO $_2$ R 13 arylalkyl, quaternary heterocycle, quaternary heteroaryl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl

 $_{P^+R^{13}R^{14}R^{15}A^-,\ P(OR^{13})OR^{14},\ S^+R^{13}R^{14}A^-,\ and\ N^+R^9R^{11}R^{12}A^-,}$ wherein:

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

aryl, haloalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, OXO, $CONR^7R^8$, $N^+R^8R^9A$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^2A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N⁴R⁷R⁸A-, S, SO, SO₂, S⁴R⁷A-, PR⁷, P(O)R⁷, P⁴R⁷R⁸A-, or phenylene, and Rl³, Rl⁴, and Rl⁵ are independently selected from the group consisting of hydrogen, alkyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, heteroaryl, quaternary heterocycly, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, alkylaminocarbonylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by 0, NR', N * R 9 R 10 A-, S, SO, SO $_{2}$ S, S * R, pR 9 , p * PR 9 R 10 A-, P(0)R', phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

 R^{13} , R^{14} , and R^{15} are optionally substituted with

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one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, oR⁹, NR⁹R¹⁰, N*R⁹R^{11R¹²A⁻, SR⁹, S(O)R⁹,}

 ${
m So_2NR^9R^{10}}$, ${
m Po(OR^{16})OR^{17}}$, ${
m P^{+}R^9R^{10}R^{14}}$ -, ${
m S^{+}R^9R^{10}}$ -, and C(0)OM, wherein ${
m R^{16}}$ and ${
m R^{17}}$ are independently selected from

SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM,

the substituents constituting R^9 and M_2 or R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 $\rm R^{14}$ and $\rm R^{15}$, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $\ensuremath{\mathrm{R}^{7}}$ and $\ensuremath{\mathrm{R}^{8}}$ are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³,

COR¹³, OR¹⁸, S(O)_DNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻ ${\rm NR}^{13}{\rm OR}^{14}$, ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$, ${\rm NO}_2$, ${\rm CO}_2{\rm R}^{13}$, CN, OM, SO2OM, $_{\rm P}^{+}{
m R}^{9}{
m R}^{11}{
m R}^{12}{
m A}^{-}$, amino acid, peptide, polypeptide, and $SO_2NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, $C(0)NR^{13}R^{14}$, NR14C(0)R13, C(0)OM $NR^{13}R^{14}$, SR^{13} , $S(0)R^{13}$, $S(0)2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$,

 $P_{R}^{+}P_{R}^{11}R_{R}^{12}A_{-}^{-}$, $S_{R}^{+}P_{R}^{10}A_{-}^{-}$, or C(0)0M, and halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷ $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, OXO_{4} , OXO_{4} heteroaryl can be further substituted with OR 9 , NR 9 R 10 polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl

acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, wherein R^{18} is selected from the group consisting of

 SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM, SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO3R9 consisting of OR9, NR9R10, N+R9R11R12A-, SR9, S(O)R9, one or more substituents selected from the group and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

peptide, polypeptide, carbohydrate, polyether, or PR^{13} , $P(0)R^{13}$, $P+R^{13}R^{14}A$ -, phenylene, amino acid, replaced by 0, NR^{13} , $N^{+}R^{13}R^{14}A^{-}$, s, s0, s02, $S^{+}R^{13}A^{-}$, wherein in RX, one or more carbons are optionally

wherein in said polyalkyl, phenylene, amino acid

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so, so₂, s⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(0)R⁹; carbons are optionally replaced by 0, NR 9 , N $^+$ R 9 R 1 0A $^-$, S, peptide, polypeptide, and carbohydrate, one or more

 ${\tt P(OR^{13})OR^{14},\ S^+R^{13}R^{14}A^-,\ and\ N^+R^9R^{11}R^{12}A^-,\ or}$ $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $P(0)R^{13}R^{14}$, $P^{+}R^{13}R^{14}R^{15}A^{-}$ ${\rm NR}^{13}{\rm R}^{14}$, ${\rm SR}^{13}$, ${\rm S(0)R}^{13}$, ${\rm SO_2R}^{13}$, ${\rm SO_3R}^{13}$, ${\rm NR}^{13}{\rm OR}^{14}$, groups selected from the group consisting of alkyl, ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$, ${\rm NO}_2$, ${\rm CO}_2{\rm R}^{13}$, ${\rm CN}$, ${\rm OM}$, ${\rm SO}_2{\rm OM}$, ${\rm SO}_2{\rm NR}^{13}{\rm R}^{14}$, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³ heteroaryl are optionally substituted with one or more prodrug thereof. alkenyl, alkynyl, polyalkyl, polyather, aryl, haloalkyl, a pharmaceutically acceptable salt, solvate, or wherein quaternary heterocycle and quaternary

carboxyalkylaminocarbonylalkyl; and alkylheterocyclylalkyl, and consisting of alkylarylalkyl, alkylheteroarylalkyl, R134 is independently selected from the group R's is phenyl substituted with OR114 2. A compound of claim 1 wherein:

heterocycle, quaternary heteroaryl, and NR[‡]R¹⁰. selected from the group consisting of carboxy, quaternary R134 is optionally substituted with one or more groups

- A compound of claim 1 wherein n is 1 or 2.
- hydrogen and alkyl. independently selected from the group consisting of 4. A compound of claim 1 wherein R' and R' are

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5. A compound of claim 1 wherein \mathbb{R}^1 and \mathbb{R}^8 are hydrogen.

- 6. A compound of claim 1 wherein R^1 and R^4 are independently selected from the group consisting of hydrogen and $\text{OR}^3\,.$
- 7. A compound of claim 1 wherein R^3 is hydrogen and R^4 is hydroxy.
- 8. A compound of claim 1 wherein one or more R^{\star} are independently selected from the group consisting of OR^{11} and $NR^{11}R^{1\star}$.
- 9. A compound of claim 1 wherein one or more $\mathbb{R}^{\mathtt{A}}$ are independently selected from methoxy and dimethylamino.
- 10. A compound of claim 1 wherein R¹ and R² are independently selected from the group consisting of hydrogen and alkyl.
- 11. A compound of claim 1 wherein R^1 and R^2 are independently selected from the group consisting alkyl.
- 12. A compound of claim 1 wherein \mathbb{R}^1 and \mathbb{R}^2 are the same alkyl.
- 13. A compound of claim 1 wherein R^1 and R^2 are each n-butyl. , $^\prime$
- 14. A compound of claim 1 wherein
- ia 1 or 2.
- R' and R' are n-butyl;
- R' and R' are hydrogen;
- is hydroxy;

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R' and R' are hydrogen; and one or more R' are independently selected from methoxy and dimethylamino.

15. A compound of claim 1 having the structural formula:

16. A compound of claim 1 having the structural formula:

17. A compound of claim 1 having the structural

formula:

21. A compound selected from the group consisting of:

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18. A compound of claim 1 having the structural 270

formula:

19. A compound of claim 1 having the structural

formula: 20. A compound of claim 1 having the structural

R = PEG 1000

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CH₃SO₃

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Meyn Meyn

쁄

and

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22. A compound of formula (I):

$$\begin{array}{c|c}
 & & & & \\
\hline
(R^{*})_{q} & & & & \\
\hline
(R^{*})_{q} & & & & \\
\hline
R^{*} & & & & \\
R^{*} & & & \\
R^{*} & & & \\
R^{*} & & & & \\
R^{*} & & & \\
R^{$$

Ξ

wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

alkylthio, (polyalkyl)aryl, and cycloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, \mathbb{R}^1 and \mathbb{R}^2 are independently selected from the group

the group consisting of cr^9 , vr^9r^{10} , $vr^9r^{10}r^wa^-$, sr^9 , substituted with one or more substituents selected from alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, wherein alkyl, alkenyl, alkynyl, haloalkyl,

S'R'R'B'. P'R9R10R11A', S(O)R9, SO2R9, SO3R9, CO2R9, CN, halogen, oxo, and CONR⁹R¹⁰, wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR^9 , $N^+R^9R^{10}A^-$, s, so, so₂, s⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, or phenylene,

from the group consisting of H, alkyl, alkenyl, alkynyl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, wherein R^9 , R^{10} , and R^w are independently selected cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

 ${\bf R}^1$ and ${\bf R}^2$ taken together with the carbon to which

 $^{\rm J}$ R $^{\rm J}$ and R $^{\rm 4}$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , $\mathrm{NR}^9\mathrm{R}^{10}$, SR^9 , $\mathrm{S}(\mathrm{O})\mathrm{R}^9$, $\mathrm{SO}_2\mathrm{R}^9$, and $\mathrm{SO}_3\mathrm{R}^9$, wherein R and R are as defined above; or they are attached form C,-C, cycloalkyl;

 $m R^3$ and $m R^4$ together form =0, =NOR 11 , =S, =NNR $^{11}
m R^{1}$ =NR9, or =CR¹¹R¹²,

the group consisting of H, alkyl, alkenyl, alkynyl, aryl, defined above, provided that both \mathbb{R}^3 and \mathbb{R}^4 cannot be OH, wherein \mathbb{R}^{11} and \mathbb{R}^{12} are independently selected from carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, halogen, oxo, and ${\rm CONR}^9{\rm R}^{10}$, wherein ${\rm R}^9$ and ${\rm R}^{10}$ are as arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, or9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN,

 ${\mathbf R}^{11}$ and ${\mathbf R}^{12}$ together with the nitrogen or carbon

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atom to which they are attached form a cyclic ring;

R⁵ is aryl substituted with one or more OR^{13b}

quaternary heterocyclylalkyl, quaternary heteroarylalkyl, wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary

 \mathbb{R}^{13b} is substituted with one or more groups selected from the group consisting of carboxyalkyl, heterocycle, heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, or guanidinyl, and

alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, S(0)R⁹, SO₂R⁹, and ${\rm R}^6$ is selected from the group consisting of H,

 ${
m SO_2OM}$, ${
m SO_2NR^{13}R^{14}}$, ${
m C(0)\,NR^{13}R^{14}}$, ${
m C(0)\,OM}$, ${
m COR^{13}}$, ${
m NR^{13}C(0)\,R^{14}}$ arylalkyl, quaternary heterocycle, quaternary heteroaryl, substituent groups independently selected from the group p+R13R14R15A, p(OR13)OR14, S+R13R14A, and N+R9R11R12Awherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, NR13C(0) NR14R15, NR13CO2R14, OC(0) R13, OC(0) NR13R14, NR13SOR14 polyether, aryl, haloalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heterocycle, and quaternary SO3R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, consisting of alkyl, alkenyl, alkynyl, polyalkyl, heteroaryl can be substituted with one or more $NR^{13}SO_{3}R^{14}$, $NR^{13}SONR^{14}R^{13}$, $NR^{13}SO_{3}NR^{14}R^{15}$, $P(O)R^{13}R^{14}$,

 ${\tt A}^{ op}$ is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, MR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, CO₂R⁷, CN, oxo, CONR⁷R⁸, N⁴R⁷R⁸A⁸, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, p(O)R⁷R⁸, p⁴R⁷R⁸R⁹A⁻, and p(O) (OR⁷)OR⁸, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR, NR, RBA-, S, SO, SO2, ST, A-, PR, P(O)R, PR, RA-, or phenylene, and R13, R14, and R15 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, heterocycle, heteroaryl, quaternary heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, dusternary heterocyclylalkyl, dusternary heterocyclylalkyl, dusternary heterocyclylalkyl, alkylaminocarbonylalkyl, alkylaminocarbonylalkyl, alkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR*, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A-, P(O)R*, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

 $\rm R^{13}, \rm R^{14},$ and $\rm R^{15}$ are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl,

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heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, oR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R¹¹A-, S⁺R⁹R¹⁰A-, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R¹¹ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R¹⁴ and R¹⁵, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $\ensuremath{R^7}$ and $\ensuremath{R^8}$ are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)2R¹³, SO₃R¹³, S⁺R¹³R¹⁴A-, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM,

 $SO_2NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, $C(0)NR^{13}R^{14}$, NR14C(0)R13, C(0)OM, COR¹³, OR¹⁸, S(O)_DNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻, $p^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

4*R9R11R12A-, SR9, S(0)R9, SO2R9, SO3R9, OXO, CO2R9, CN, heteroaryl can be further substituted with OR^9 , $\mathrm{NR}^9\mathrm{R}^{10}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷ +R9R11R12A-, S+R9R10A-, or C(0) OM, and wherein $\ensuremath{\text{R}}^{18}$ is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO3R⁹, consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, wherein acyl, arylalkoxycarbonyl, arylalkyl, one or more substituents selected from the group SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(0)OM,

wherein in \mathbb{R}^{X} , one or more carbons are optionally replaced by O, NR¹³, N⁺R¹³R¹⁴A-, S, SO, SO₂, S⁺R¹³A⁻, peptide, polypeptide, carbohydrate, polyether, or PR¹³, P(O)R¹³, P⁺R¹³R¹⁴A-, phenylene, amino acid,

carbons are optionally replaced by 0, NR9, N+R9R10A-, S, wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more

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so, so2, s+R3A-, PR3, P+R3R10A-, or P(O)R3;

alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, heteroaryl are optionally substituted with one or more $c(0) NR^{13}R^{14}$, c(0) OM, cOR^{13} , $P(O) R^{13}R^{14}$, $P^{+}R^{13}R^{14}R^{15}A^{-}$, a pharmaceutically acceptable salt, solvate, or NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, groups selected from the group consisting of alkyl, wherein quaternary heterocycle and quaternary NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, P(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻, or prodrug thereof.

consisting of alkyl, quaternary heteroarylalkyl, and R^{110} is independently selected from the group 23. A compound of claim 22 wherein: R' is phenyl substituted with OR118, quaternary heterocyclylalkyl; and

from the group consisting of heterocycle, heterosryl, and R^{13b} is substituted with one or more groups selected guanidinyl.

- 24. A compound of claim 22 wherein n is 1 or 2.
- 25. A compound of claim 22 wherein R' and R' are independently selected from the group consisting of hydrogen and alkyl.
- A compound of claim 22 wherein R' and R' are hydrogen.
- 27. A compound of claim 22 wherein R1 and R4 are independently selected from the group consisting of

hydrogen and OR'.

- 28. A compound of claim 22 wherein \mathbb{R}^{1} is hydrogen and
- and NR"R". independently selected from the group consisting of \mathbb{OR}^{13} 29. A compound of claim 22 wherein one or more R* are
- independently selected from methoxy and dimethylamino. 30. A compound of claim 22 wherein one or more R* are
- hydrogen and alkyl. independently selected from the group consisting of 31. A compound of claim 22 wherein R and R are
- independently selected from the group consisting alkyl. 32. A compound of claim 22 wherein \mathbb{R}^1 and \mathbb{R}^2 are
- 33. A compound of claim 22 wherein R' and R' are the
- n-butyl. 34. A compound of claim 22 wherein R and R are each
- 35. A compound of claim 22 wherein

n is 1 or 2;

R' and R' are n-butyl;

R' and R' are hydrogen;

R' is hydroxy;

R' and R' are hydrogen; and

and dimethylamino. one or more $R^{\mathbf{x}}$ are independently selected from methoxy

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36. A compound of claim 22 having the structural

A compound of claim 22 having the structural

A compound of formula (I):

Ξ

wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R¹ and R² are independently selected from the group alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylthio, (polyalkyl) aryl, and cycloalkyl,

alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, substituted with one or more substituents selected from the group consisting of $\mathrm{OR}^9,\ \mathrm{NR}^9\mathrm{R}^{10},\ \mathrm{N}^4\mathrm{R}^9\mathrm{R}^{10}\mathrm{R}^\mathrm{M}^4^-,\ \mathrm{SR}^9,$ $S'R^3R^3G$. $P^+R^9R^{10}R^{11}A^-$, $S(0)R^9$, So_2R^9 , So_3R^9 , Co_2R^9 , CN, wherein alkyl, alkenyl, alkynyl, haloalkyl, halogen, oxo, and CONR9R10,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, ${
m NR}^9$, ${
m N}^4{
m R}^9{
m R}^{10}{
m A}^-$, s, so, so₂, s⁺R⁹A', p⁺R⁹R¹⁰A', or phenylene,

from the group consisting of H, alkyl, alkenyl, alkynyl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, wherein R^9 , R^{10} , and R^{W} are independently selected cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

 R^{1} and R^{2} taken together with the carbon to which they are attached form C,-C, cycloalkyl; R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R' and R' are as defined above; or

R³ and R⁴ together form =0, =NOR¹¹, =S, =NNR¹¹R¹²,

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the group consisting of H, alkyl, alkenyl, alkynyl, aryl, wherein \mathbb{R}^{11} and \mathbb{R}^{12} are independently selected from carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, halogen, oxo, and ${\rm CONR}^9{\rm R}^{10}$, wherein ${\rm R}^9$ and ${\rm R}^{10}$ are as arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, OR9, NR9R10, SR9, S(0)R9, SO2R9, SO3R9, CO2R9, CN,

 R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

defined above, provided that both R^3 and R^4 cannot be OH.

NH, and SH, or

R⁵ is aryl substituted with one or more OR^{13b},

quaternary heterocyclylalkyl, quaternary heteroarylalkyl, wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkoxyalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, $m R^{13b}$ is substituted with one or more groups selected from the group consisting of OR 9a , NR 9a R 10 , N $^{+}$ R 9a R 11 R 12 A $^{-}$, sr^{9a}, s(o)r^{9a}, so₂r^{9a}, so₃r^{9a}, co₂r^{9a}, conr^{9a}r¹⁰, SO2NR9aR10, P+R9aR10R11A-, and S+R9aR10A-,

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, and

wherein $R^{\mbox{\scriptsize 9a}}$ is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, and carboxyalkylaminoalkyl;

quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, ${{\mathsf R}}^6$ is selected from the group consisting of H,

polyether, aryl, haloalkyl, cycloalkyl, heterocycle, $NR^{13}C(0)NR^{14}R^{15}$, $NR^{13}CO_{2}R^{14}$, $OC(0)R^{13}$, $OC(0)NR^{13}R^{14}$, $NR^{13}SOR^{14}$ SO_2OM , $SO_2NR^{13}R^{14}$, $C(0)NR^{13}R^{14}$, C(0)OM, COR^{13} , $NR^{11}C(0)R^{14}$, arylalkyl, quaternary heterocycle, quaternary heteroaryl, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heteroaryl can be substituted with one or more heterocycle, quaternary heterocycle, and quaternary $_{\rm P}^{+}{}_{\rm R}^{13}{}_{\rm R}^{14}{}_{\rm R}^{15}{}_{\rm A}^{-}$, $_{\rm P}^{({
m OR}^{13})}{}_{\rm OR}^{14}$, $_{\rm S}^{+}{}_{\rm R}^{13}{}_{\rm R}^{14}{}_{\rm A}^{-}$, and $_{\rm N}^{+}{}_{\rm R}^{9}{}_{\rm R}^{11}{}_{\rm R}^{12}{}_{\rm A}^{-}$ NR1150,R14, NR1150NR14R15, NR1150,NR14R15, P(0)R13R14, $_{
m SO_3R^{13}}$, $_{
m NR^{13}OR^{14}}$, $_{
m NR^{13}NR^{14}R^{15}}$, $_{
m NO_2}$, $_{
m CO_2R^{13}}$, $_{
m CN}$, $_{
m OM_2}$ halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³ wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl

pharmaceutically acceptable cation, \mathtt{A}^{-} is a pharmaceutically acceptable anion and M is a

 $P(0)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(0)(0R^7)OR^8$, and arylalkyl, quaternary heterocycle, quaternary heteroaryl $s(o)R^7$, so_2R^7 , so_3R^7 , co_2R^7 , cn, oxo, $conR^7R^8$, $N^4R^7R^8R^9A$ selected from the group consisting of OR 7 , NR 7 R 8 , SR 7 , aryl, haloalkyl, cycloalkyl, and heterocycle can be polyether, aryl, haloalkyl, cycloalkyl, and heterocycle further substituted with one or more substituent groups , alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle said alkyl, alkenyl, alkynyl, polyalkyl, polyether, wherein said alkyl, alkenyl, alkynyl, polyalkyl,

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alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, alkylarylalkyl, alkylheteroarylalkyl, NR^7 , $N^+R^7R^8A^-$, s, so, so₂, $S^+R^7A^-$, PR^7 , $P(0)R^7$, $P^+R^7R^8A^$ quaternary heterocyclylalkyl, quaternary heteroarylalkyl heteroaryl, heterocyclylalkyl, heteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl selected from the group consisting of hydrogen, alkyl, or phenylene, and \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are independently heteroaryl, quaternary heterocycle, quaternary can optionally have one or more carbons replaced by 0, wherein alkyl, alkenyl, alkynyl, arylalkyl,

 $_{PR}^{9}$, $_{P}^{+}_{R}^{9}_{R}^{10}_{A}$ -, $_{P}(0)_{R}^{\bullet}$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are optionally substituted with

carbons replaced by 0, NR, N $^+$ R 9 R 10 A-, S, SO, SO $_2$, S $^+$ R 9 A $^$ heterocycle, and polyalkyl optionally have one or more

 $\mathrm{SO_2R}^9$, $\mathrm{SO_3R}^9$, oxo , $\mathrm{CO_2R}^9$, CN , $\mathrm{halogen}$, $\mathrm{CONR}^9\mathrm{R}^{10}$, $\mathrm{SO_2OM}$ guanidinyl, or⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, heterocycle, quaternary heteroaryl, quaternary heterocycle, heteroaryl, sulfoalkyl, quaternary one or more groups selected from the group consisting of ${
m SO_2NR^9R^{10}}$, ${
m PO(OR^{16})OR^{17}}$, ${
m P^+R^9R^{10}R^{11}A^-}$, ${
m S^+R^9R^{10}A^-}$, and heterocyclylalkyl, quaternary heteroarylalkyl hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl,

the substituents constituting R^9 and M; or wherein $\mathbf{R}^{\mathbf{16}}$ and $\mathbf{R}^{\mathbf{17}}$ are independently selected from

that is optionally substituted with one or more radicals they are attached form a mono- or polycyclic heterocycle R" and R", together with the nitrogen atom to which

 $\rm R^{14}$ and $\rm R^{15},$ together with the nitrogen atom to which they are attached, form a cyclic ring; and

R is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, heterocyclylalkyl, and alkylammoniumalkyl; and ammoniumalkyl, alkylammoniumalkyl, arylalkyl,

 $\ensuremath{\mathrm{R}^{7}}$ and $\ensuremath{\mathrm{R}^{8}}$ are independently selected from the group consisting of hydrogen and alkyl; and

SO2NR¹³R¹⁴, NR¹⁴C(0)R¹³, C(0)NR¹³R¹⁴, NR14C(0)R13, C(0)OM, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, one or more R^{X} are independently selected from the \cos^{13} , \cos^{18} , $s(o)_{n}$ NR^{18} , NR^{13} R^{18} , NR^{18} OR^{14} , N^{+} R^{9} R^{11} R^{12} A^{-} $^{13}R^{14}$, 13 , 13 , 13 , 13 , 13 , $^{14}A^{-}$, quaternary heterocycle, quaternary heteroaryl, OR^{13} , NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, cycloalkyl, heterocycle, heteroaryl, polyether, group consisting of H, alkyl, alkenyl, alkynyl,

"*R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, OXO, CO₂R⁹, CN, heteroaryl can be further substituted with $exttt{OR}^9$, $exttt{NR}^9 exttt{R}^{10}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁵)OR¹⁷ P+R9R11R12A-, S+R9R10A-, or C(0) OM, and

 $p^{+}R^{9}R^{11}R^{12}A^{-}$, amino acid, peptide, polypeptide, and

carbohydrate,

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wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO3R⁹, consisting of OR^9 , N^9R^{10} , $N^4R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, wherein acyl, arylalkoxycarbonyl, arylalkyl, one or more substituents selected from the group $\mathrm{SO_2OM}$, $\mathrm{SO_2NR^9R^{10}}$, $\mathrm{PO\left(OR^{16}\right)OR^{17}}$, and $\mathrm{C\left(O\right)OM}$,

wherein in \mathbb{R}^{X} , one or more carbons are optionally replaced by O, NR^{13} , $\mathrm{N}^+\mathrm{R}^{13}\mathrm{R}^{14}\mathrm{A}^-$, S, SO, SO2, $\mathrm{S}^+\mathrm{R}^{13}\mathrm{A}^$ peptide, polypeptide, carbohydrate, polyether, or PR^{13} , $P(0)R^{13}$, $P^{+}R^{13}R^{14}A^{-}$, phenylene, amino acid,

carbons are optionally replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, S, wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more so, so2, s+R3A-, PR3, P+R3R10A-, or P(O)R3;

alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{l3}, heteroaryl are optionally substituted with one or more C(0) NR¹³R¹⁴, C(0) OM, COR¹³, P(0) R¹³R¹⁴, P⁺R¹³R¹⁴R¹⁵A⁻ groups selected from the group consisting of alkyl, ${
m NR}^{13} {
m NR}^{14} {
m R}^{15}$, NO2, ${
m CO}_2 {
m R}^{13}$, CN, OM, ${
m SO}_2 {
m OM}$, ${
m SO}_2 {
m NR}^{13} {
m R}^{14}$ wherein quaternary heterocycle and quaternary ${
m NR}^{13}{
m R}^{14}$, ${
m SR}^{13}$, ${
m S(0)}{
m R}^{13}$, ${
m SO}_2{
m R}^{13}$, ${
m SO}_3{
m R}^{13}$, ${
m NR}^{13}{
m OR}^{14}$, P(OR13)OR14, S+R13R14A-, and N+R9R11R12A-, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

39. A compound of claim 38 wherein:

R's is phenyl substituted with OR115;

 R^{10} is selected from the group consisting of alkyl and alkoxyalkyl; and

 R^{13b} is substituted with one or more groups selected from the group consisting of \mbox{OR}^{9n} and $\mbox{NR}^{9n}\mbox{R}^{10}$; and

R⁹⁴ is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, and carboxyheterocycle; and

R10 is carboxyalkyl.

- 0. A compound of claim 38 wherein n is 1 or 2.
- 41. A compound of claim 38 wherein \mathbb{R}^7 and \mathbb{R}^8 are independently selected from the group consisting of hydrogen and alkyl.
- 42. A compound of claim 38 wherein R^2 and R^4 are hydrogen.
- 43. A compound of claim 38 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^3 .
- 44. A compound of claim 38 wherein R^{λ} is hydrogen and R^{λ} is hydroxy.
- 45. A compound of claim 38 wherein one or more R^{\star} are independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$.
- 46. A compound of claim 38 wherein one or more R^{x} are independently selected from methoxy and dimethylamino.

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- 47. A compound of claim 38 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl.
- 48. A compound of claim 38 wherein R^1 and R^2 are independently selected from the group consisting alkyl.
- 49. A compound of claim 38 wherein \mathbb{R}^1 and \mathbb{R}^2 are the same alkyl.
- 50. A compound of claim 38 wherein R^1 and R^2 are each n-butyl.
- 51. A compound of claim 38 wherein

n is 1 or 2;

R' and R' are n-butyl;

R' and R' are hydrogen;

R' is hydroxy;

R' and R' are hydrogen; and

one or more R^{\star} are independently selected from methoxy and dimethylamino.

52. A compound of claim 38 having the structural formula:

296 53. A compound of claim 38 having the structural

formula:

 f_{\star}^{\dagger} :54. A compound of claim 38 having the structural formula:

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55. A compound of formula (I):

E

wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^M^A, SR⁹, S'R⁹R⁹, P⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR 9 , N 4 R 9 R 1 O $_4$, S, SO, SO $_2$, S 4 R 9 R, P 4 R 9 R 1 O $_4$, or phenylene,

wherein $\rm R^9$, $\rm R^{10}$, and $\rm R^W$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl,

heteroarylalkyl, heterocyclylalkyl, and carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino alkylammoniumalkyl; or

they are attached form C3-C10 cycloalkyl; \mathbb{R}^1 and \mathbb{R}^2 taken together with the carbon to which

heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(O)R⁹, SO₂R⁹, and SO₃R⁹ wherein R'and R'are as defined above; or consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl R³ and R⁴ are independently selected from the group

"NR9, or =CR11R12, $m R^3$ and $m R^4$ together form =0, =NOR 11 , =S, =NNR $^{11}
m R^{12}$

 OR^9 , NR^9R^{10} , SR^9 , $S(0)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as the group consisting of H, alkyl, alkenyl, alkynyl, aryl NH₂, and SH, or defined above, provided that both R^3 and R^4 cannot be OH. wherein R^{11} and R^{12} are independently selected from

atom to which they are attached form a cyclic ring; R¹¹ and R¹² together with the nitrogen or carbon ${\tt R}^{\tt 5}$ is aryl substituted with one or more ${\tt OR}^{\tt 13b}$

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkylheterocyclylalkyl, cycloalkyl, heterocycle, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, wherein R^{13b} is selected from the group consisting

is substituted with one or more groups selected

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carboxyalkylheterocyclylthio, NR^9R^{10a} , $CONR^9R^{10a}$ $SO_{2}NR^{9}R^{10a}$, $P^{+}R^{9}R^{10a}R^{11}A^{-}$, and $S^{+}R^{9}R^{10a}A^{-}$, from the group consisting of

and M is a pharmaceutically acceptable cation, wherein A is an pharmaceutically acceptable anion

heteroarylalkyl, and heterocyclylalkyl; or of carboxyalkyl, carboalkoxyalkyl, carboxyalkylamino wherein R^{10a} is selected from the group consisting

quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, \mathbb{R}^6 is selected from the group consisting of H,

 $_{p}^{+}$ $_{R}^{13}$ $_{R}^{14}$ $_{R}^{15}$ $_{A}^{-}$, $_{p}$ (or $_{p}^{13}$) or $_{p}^{14}$, $_{S}^{+}$ $_{R}^{13}$ $_{R}^{14}$ $_{A}^{-}$, and $_{R}^{+}$ $_{R}^{11}$ $_{R}^{12}$ $_{A}^{-}$ NR11502R14, NR1150NR14R15, NR11502NR14R15, P(0)R13R14, NR13C(0)NR14R15, NR13CO,R14, OC(0)R13, OC(0)NR13R14, NR13SOR14, arylalkyl, quaternary heterocycle, quaternary heteroaryl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heteroaryl can be substituted with one or more so_2om , $so_2nr^{13}r^{14}$, $c(o)nr^{13}r^{14}$, c(o)om, cor^{13} , $nr^{13}c(o)r^{14}$ SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(0)R^{13}$, SO_2R^{13} heterocycle, quaternary heterocycle, and quaternary wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl

pharmaceutically acceptable cation, ${\tt A}^{ ilde{{}}}$ is a pharmaceutically acceptable anion and M is said alkyl, alkenyl, alkynyl, polyalkyl, polyether,

aryl, haloalkyl, cycloalkyl, and heterocycle can be

further substituted with one or more substituent groups selected from the group consisting of OR7, NR7R8, SR7, S(O)R7, SO2R7, SO2R7, CM, OXO, CONR7R8, N*R7R8R9A-, alkyl, alkenyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, P(O)R7R8, p*R7R8R9A-, and P(O)(OR7)OR8, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R⁷, P⁺R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylheteroarylalkyl, heterocyclylalkyl, cycloalkyl, heterocycle, heterocyclylalkyl, heterocycle, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by 0, NR', $N^{+}R^{10}A^{-}$, S, SO, SO2, $S^{+}R^{3}A$, PR 9 , $p^{+}R^{9}R^{10}A^{-}$, $p(0)R^{*}$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R13, R14, and R15 are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, OR9, NR9R10, N+R9R11R12A-, SR9, S(O)R9,

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SO2R⁹, SO3R⁹, OXO, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO2OM, SO2NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R¹¹R-, S⁺R⁹R¹⁰R-, and

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M, or

R¹³ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 $\rm R^{14}$ and $\rm R^{15}$, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R³⁰ is selected from the group consisting of alkyl, alkynl, alkynl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

 $\ensuremath{\mathrm{R}}^7$ and $\ensuremath{\mathrm{R}}^8$ are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, S(0)₂R¹³, SO₃R¹³, S⁺R¹³R¹⁴A₋, NR¹³OR¹⁴, NR¹³OR¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C(0)R¹³, C(0) NR¹³R¹⁴, NR¹⁴C(0)R¹³, C(0) OM, COR¹³, OR¹⁸, S(0)_NNR¹³R¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A₋, p⁺R⁹R¹¹R¹²A₋, amino acid, peptide, polypeptide, and

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carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰A⁻, or C(0)OM, and

wherein \mathbb{R}^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N*R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₃R⁹, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, and C(O)OM,

wherein in R^X , one or more carbons are optionally replaced by 0, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO₂, $S^+R^{13}A^-$, PR^{13} , $P(0)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, S, SO, SO₂, S⁺R⁹A-, PR⁹, P⁺R⁹R¹⁰A-, or P(O)R⁹;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,

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alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , SO_1R^{13} , SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13} , $P(O)R^{13}R^{14}$, $P+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S+R^{13}R^{14}A^-$, and $N+R^{9}R^{11}R^{12}A^-$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

56. A compound of claim 55 wherein:

R^{\$} is phenyl substituted with OR¹¹⁵;

R¹¹⁶ is alkyl; and

R¹¹⁶ is substituted with carboxyalkylheterocyclylthio or NR^{\$}R¹⁰⁶; and

R^{\$} is hydrogen; and

57. A compound of claim 55 wherein n is 1 or 2.

R10 is heteroarylalkyl.

- 58. A compound of claim 55 wherein R² and R⁴ are independently selected from the group consisting of hydrogen and alkyl.
- 59. A compound of claim 55 wherein R' and R' are hydrogen.
- 60. A compound of claim 55 wherein R^{\star} and R^{\star} are independently selected from the group consisting of hydrogen and OR^{\star} .
- 61. A compound of claim 55 wherein $\ensuremath{R^{\prime}}$ is hydrogen and $\ensuremath{R^{\prime}}$ is hydroxy.

62. A compound of claim 55 wherein one or more $\ensuremath{R^{\kappa}}$ are independently selected from the group consisting of OR¹³ and NR11R14.

- 63. A compound of claim 55 wherein one or more $\boldsymbol{R}^{\boldsymbol{x}}$ are independently selected from methoxy and dimethylamino.
- 64. A compound of claim 55 wherein $R^1 \ and \ R^2 \ are$ independently selected from the group consisting of hydrogen and alkyl.
- independently selected from the group consisting alkyl. 65. A compound of claim 55 wherein R¹ and R² are
- 66. A compound of claim 55 wherein R' and R' are the same alkyl.
- 67. A compound of claim 55 wherein \boldsymbol{R}^1 and \boldsymbol{R}^2 are each n-butyl.
- 68. A compound of claim 55 wherein
 - n is 1 or 2;
- R' and R' are n-butyl; R' and R' are hydrogen;
- R' is hydroxy;
- R' and R' are hydrogen; and

one or more R' are independently selected from methoxy and dimethylamino.

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A compound of claim 55 having the structural formula:

A compound of claim 55 having the structural formula: 70.

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compound of formula (I):

 $\begin{array}{c|c}
(R^n)_q & & \\
\hline
(R^n)_q & & \\
(R^n)_q & & \\
\hline
(R^n)_q & & \\
(R^n)_q & & \\$

Ξ

wherein:

q is an integer from 1 to 4; n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^WA⁻, SR⁹, S'R'R'A: p⁺R⁹R¹⁰R¹¹A⁻, S(0)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹, N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, or phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl,

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carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

 $\rm R^1$ and $\rm R^2$ taken together with the carbon to which they are attached form $\rm C_3-\rm C_{10}$ cycloalkyl;

 $\rm R^3$ and $\rm R^4$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR⁹, NR⁹R¹⁰, SR⁹, S(0)R⁹, SO₂R⁹, and SO₃R⁹, wherein R⁹ and R¹⁰ are as defined above; or

 $\rm R^3$ and $\rm R^4$ together form =0, =NOR 11 , =5, =NNR $^{11}\rm R^{12}$, =NR 9 , or =CR $^{11}\rm R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkenylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, CR^9 , CR^9 ,

 $\rm R^{11}$ and $\rm R^{12}$ together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R⁵ is aryl substituted with one or more substituent groups independently selected from the group consisting of NR¹³C(O)R¹⁴, NR¹³C(O)NR¹⁴R¹³, NR¹³CO₂R¹⁴, OC(O)R¹³, OC(O)NR¹³R¹⁴, NR¹³SOR¹⁴, NR¹³SO₂R¹⁴, NR¹³SONR¹⁴R¹³, and NR¹³SO₄NR¹⁴R¹³,

wherein:

R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylheteroarylalkyl,

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quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary

one or more groups selected from the group consisting of SO2R⁹, SO3R⁹, oxo, CO2R⁹, CN, halogen, CONR⁹R¹⁰, SO2OM, R¹³, R¹⁴, and R¹⁵ are optionally substituted with SO2NR9R10, PO(OR16)OR17, P+R9R10R11A-, S+R9R10A-, and hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, guanidinyl, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl,

wherein A is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein ${
m R}^{16}$ and ${
m R}^{17}$ are independently selected from the substituents constituting \mathbb{R}^9 and M; or

R" and R", together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 R^{14} and $\mathrm{R}^{15},$ together with the nitrogen atom to which they are attached, form a cyclic ring; and

alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^{9} , $S(O)R^{9}$, SO_2R^{9} , and R^6 is selected from the group consisting of H,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

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 ${
m SO_2OM}$, ${
m SO_2NR^{13}R^{14}}$, C(0) ${
m NR^{13}R^{14}}$, C(0) OM, ${
m COR^{13}}$, ${
m NR^{13}C(0)R^{14}}$, $p^{+}R^{13}R^{14}R^{15}A^{-}$, $p(0R^{13})0R^{14}$, $S^{+}R^{13}R^{14}A^{-}$, and $N^{+}R^{9}R^{11}R^{12}A^{-}$, arylalkyl, quaternary heterocycle, quaternary heteroaryl, substituent groups independently selected from the group $NR^{13}C(0)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(0)R^{13}$, $OC(0)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, neterocycle, quaternary heterocycle, and quaternary SO3R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO2, CO₂R¹³, CN, OM, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³ consisting of alkyl, alkenyl, alkynyl, polyalkyl, heteroaryl can be substituted with one or more NR¹¹SO₂R¹⁴, NR¹¹SONR¹⁴R¹⁵, NR¹¹SO₂NR¹⁴R¹⁵, P(O)R¹³R¹⁴,

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein:

S(0)R7, SO2R7, SO3R7, CO2R7, CN, OXO, CONR7R8, N*R7R8R9A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, said alkyl, alkenyl, alkynyl, polyalkyl, polyether, further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , aryl, haloalkyl, cycloalkyl, and heterocycle can be P(0)R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(0) (OR⁷)OR⁸, and

NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R⁷, P⁺R⁷R⁸A-, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, selected from the group consisting of hydrogen, alkyl, or phenylene, and R^{13} , R^{14} , and R^{15} are independently wherein said alkyl, alkenyl, alkynyl, polyalkyl, alkylarylalkyl, alkylheteroarylalkyl,

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle quaternary heterocyclylalkyl, quaternary heteroarylalkyl heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary

pR⁹, p⁺R⁹R¹⁰A-, P(0)R⁹, phenylene, carbohydrate, amino carbons replaced by O, NR*, N[†]R⁹R¹⁰A-, S, SO, SO₂, S[†]R⁹A heterocycle, and polyalkyl optionally have one or more acid, peptide, or polypeptide, and wherein alkyl, alkenyl, alkynyl, arylalkyl,

 ${\rm SO_{2}NR^{9}R^{10}}$, ${\rm PO(OR^{16})OR^{17}}$, ${\rm P^{+}R^{9}R^{10}R^{11}A^{-}}$, ${\rm S^{+}R^{9}R^{10}A^{-}}$, and SO2R9, SO3R9, oxo, CO2R9, CN, halogen, CONR9R10, SO2OM, guanidiny1, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(0)R^9$, heterocyclylalkyl, quaternary heteroarylalkyl, heterocycle, quaternary heteroaryl, quaternary one or more groups selected from the group consisting of heterocycle, heteroaryl, sulfoalkyl, quaternary hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are optionally substituted with

the substituents constituting R^9 and M; or wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected from

selected from the group consisting of oxo, carboxy and that is optionally substituted with one or more radicals quaternary salts; or they are attached form a mono- or polycyclic heterocycle R" and R", together with the nitrogen atom to which

which they are attached, form a cyclic ring; and ${ t R}^{14}$ and ${ t R}^{15}$, together with the nitrogen atom to

alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, R" is selected from the group consisting of alkyl

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heterocyclylalkyl, and alkylammoniumalkyl; and carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle,

consisting of hydrogen and alkyl; and ${\tt R}^7$ and ${\tt R}^8$ are independently selected from the group

 $NR^{13}R^{14}$, SR^{13} , $S(0)R^{13}$, $S(0)R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^$ quaternary heterocycle, quaternary heteroaryl, OR^{13} , cycloalkyl, heterocycle, heteroaryl, polyether, group consisting of H, alkyl, alkenyl, alkynyl carbohydrate, $\rm p^+ \rm R^9 \rm R^{11} \rm R^{12} \rm A^-$, amino acid, peptide, polypeptide, and COR¹³, OR¹⁶, S(O)nWR¹⁶, WR¹³R¹⁸, WR¹⁶OR¹⁴, W*R⁹R¹¹R¹²A- $\text{SO}_{2}\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(0)\text{R}^{13}$, $\text{C}(0)\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(0)\text{R}^{13}$, C(0)OM. ${\rm NR}^{13}{\rm OR}^{14}$, ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$, ${\rm NO}_2$, ${\rm CO}_2{\rm R}^{13}$, ${\rm CN}$, ${\rm OM}$, ${\rm SO}_2{\rm OM}$ polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, one or more $R^{\mathbf{X}}$ are independently selected from the

 $P^{+}R^{9}R^{11}R^{12}A^{-}$, $S^{+}R^{9}R^{10}A^{-}$, or C(0)OM, and $_{
m N^{+}R^{9}R^{11}R^{12}A^{-}}$, sr⁹, s(0)R⁹, s0₂R⁹, s0₃R⁹, oxo, c0₂R⁹, cN polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, heteroaryl can be further substituted with OR^9 , NR^9R^{10} wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, wherein $\mathbf{R}^{\mathbf{18}}$ is selected from the group consisting of

one or more substituents selected from the group and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , $SO_3NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^{X} , one or more carbons are optionally replaced by O, NR^{13} , $N^{\dagger}R^{13}R^{14}A^{-}$, S, SO, SO₂, $S^{\dagger}R^{13}A^{-}$, PR^{13} , $P(O)R^{13}$, $P^{\dagger}R^{13}R^{14}A^{-}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalky₁,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by 0, NR 9 , N $^+$ R 9 R 10 A $^-$, S, SO, SO2, S $^+$ R 9 A $^-$, PR 9 R 1 OA $^-$, or P(O)R 9 ;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³NR¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₂R¹³, SO₂R¹³, NR¹³OR¹⁴, C(O)NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)NR¹³R¹⁴, p¹R¹³R¹⁴, p(O)R¹³R¹⁴, p¹R¹³R¹⁴, p(O)R¹³R¹⁴, p¹R¹³R¹⁴, s¹R¹³R¹⁴A², and N¹R⁹R¹¹R¹²A², or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

- 72. A compound of claim 71 wherein R^5 is aryl substituted with a radical selected from the group consisting of $NR^{13}C(0)NR^{14}R^{15}$ and $NR^{13}CO_1R^{14}$.
- 73. A compound of claim 71 wherein R⁵ is phenyl substituted with a radical selected from the group

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consisting of NR11C(0)NR14R15 and NR11CO2R14.

- 74. A compound of claim 71 wherein n is 1 or 2.
- 75. A compound of claim 71 wherein R^{\dagger} and R^{\bullet} are independently selected from the group consisting of hydrogen and alkyl.
- 76. A compound of claim 71 wherein R^{\flat} and R^{\flat} are hydrogen.
- 77. A compound of claim 71 wherein R^{\flat} and R^{\flat} are independently selected from the group consisting of hydrogen and $OR^{\flat}.$
- 78. A compound of claim 71 wherein R^2 is hydrogen and R^4 is hydroxy.
- 79. A compound of claim 71 wherein one or more R^{\star} are independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$.
- 80. A compound of claim 71 wherein one or more R^{\star} are independently selected from methoxy and dimethylamino.
- 81. A compound of claim 71 wherein R¹ and R² are independently selected from the group consisting of hydrogen and alkyl.
- 82. A compound of claim 71 wherein R^1 and R^2 are independently selected from the group consisting alkyl.

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game alkyl. 83. A compound of claim 71 wherein \mathbb{R}^1 and \mathbb{R}^2 are the

n-butyl. 84. A compound of claim 71 wherein \mathbb{R}^1 and \mathbb{R}^2 are each

85. A compound of claim 71 wherein

n is 1 or 2;

R1 and R2 are n-butyl;

R' and R' are hydrogen;

R' is hydroxy;

R' and R' are hydrogen; and

one or more $R^{\mathbf{x}}$ are independently selected from methoxy

and dimethylamino.

86. Compound of claim 71 having the structural

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87. A compound of claim 71 having the structural formula:

88. A compound of formula I:

$$(R^n)_q = \begin{pmatrix} 0 & R^n \\ 1 & R^n \\ 1 & R^n \end{pmatrix}$$

$$R^n = \begin{pmatrix} 0 & R^n \\ 1 & R^n \\ 1 & R^n \end{pmatrix}$$

$$R^n = \begin{pmatrix} 0 & R^n \\ 1 & R^n \\ 1 & R^n \end{pmatrix}$$

Ξ

wherein:

q is 1 or 2;

n is 2;

R' and R' are each alkyl;

R³ is hydroxy;

R' and R' are hydrogen;

R⁵ has the formula (II)

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(II)

wherein t is an integer from 0 to 5;

one or more R' are OR 13;

heteroaryl, quaternary heteroarylalkyl, and alkoxyalkyl; hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, alkylarylalkyl, cycloalkyl, heterocycle, ${\bf R}^{13}$ is selected from the group consisting of heteroaryl, quaternary heterocycle, quaternary

heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR', N'R'R10A, S, SO, SO, S'R'A', PR', P'R'R'A', P(0)R', phenylene, carbohydrate, said R¹³ alkyl, alkenyl, alkynyl, arylalkyl, amino acid, peptide, or polypeptide;

quaternary heterocycle, quaternary heteroaryl, OR', NR'R'°, groups selected from the group consisting of sulfoalkyl, halogen, CONR*R10, SO4OM, SO4NR*R10, PO(OR16)OR17, P*R*R10R11A, \mathbb{R}^{13} is optionally substituted with one or more N'R'R11R13A', SR', S(O)R', SO3R', SO3R', OXO, CO3R', CN, S'R'R10A', and C(O)OM,

wherein A' is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation,

R' and R' are independently selected from the group aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, alkylammoniumalkyl;

 R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl,

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provided that both R' and R' cannot be OH, NH,, and SH; or oxo, and $CONR^3R^{10}$, wherein R^3 and R^{10} are as defined above, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR', NR'R1", SR', S(O)R', SO,R', SO,R', CO,R', CN, halogen, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle,

R" and R" together with the nitrogen or carbon atom to which they are attached form a cyclic ring; and

R16 and R17 are independently selected from the substituents constituting R' and M;

R' and R' are hydrogen; and

group consisting of alkoxy, alkylamino and dialkylamino; one or more R* are independently selected from the

a pharmaceutically acceptable salt, solvate, or prodrug thereof. 89. A compound of claim 88 wherein R' and R' are each n-butyl. 90. A compound of claim 89 wherein t is 1, \mathbb{R}^{r} is OR13, and R13 is as defined in claim 88. 91. A compound of claim 90 wherein one or more R* are independently selected from methoxy and dimethylamino.

92. A compound of claim 90 wherein R is dimethylamino.

93. A compound of claim 90 wherein:

R' is para-OR"; and

94. A compound of claim 90 wherein: t 18 1;

RY is meta-OR13; and

R13 is as defined in claim 88

- configuration. 95. A compound of claim 90 having the 4R,5R
- compound of of any one of claims 1 to 95, and anti-hyperlipidemic condition effective amount of a a pharmaceutically acceptable carrier. 96. A pharmaceutical composition comprising an
- any one of claims 1 to 95, and anti-atherosclerotic effective amount of a compound of a pharmaceutically acceptable carrier 97. A pharmaceutical composition comprising an
- of any one of claims 1 to 95, and anti-hypercholesterolemia effective amount of a compound 98. A pharmaceutical composition comprising an
- a pharmaceutically acceptable carrier
- patient in need thereof a composition of claim 96 in unit hyperlipidemic condition comprising administering to a 99. A method for the prophylaxis or treatment of a
- patient in need thereof a composition of claim 97 unit dosage form. atherosclerotic condition comprising administering to a 100. A method for the prophylaxis or treatment of an
- hypercholesterolemia comprising administering to a 101. A method for the prophylaxis or treatment of

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patient in need thereof a composition of claim 98 in unit dosage form.

- prophylaxis or treatment of a hyperlipidemic condition. in the preparation of a medicament for use in the 102. Use of a compound of any one of claims 1 to 95
- prophylaxis or treatment of an atherosclerotic condition. in the preparation of a medicament for use in the 103. Use of a compound of any one of claims 1 to 95
- prophylaxis or treatment of hypercholesterolemia in the preparation of a medicament for use in the condition.

104. Use of a compound of any one of claims 1 to 95

105. A process for the preparation of a compound having the formula:

XI

comprising:

an intermediate comprising a sulfate group; and form the compound of formula XLI; removing the sulfate group of the intermediate to coupling the thiophenyl and a cyclic sulfate to form treating a thiophenol with an abstracting agent;

q is an integer from 1 to 4;

R' and R' are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR',

N'R'R'A', S, SO, SO, S'R'A', PR'R''A', or phenylene, wherein R', R'', and R' are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylatyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, carboxyalkylaminoalkyl, heteroarylalkyl,

heterocyclylalkyl, and alkylammoniumalkyl; or R¹ and R² taken together with the carbon to which they are attached form C₁-C₁o cycloalkyl;

R' is hydroxy;

R' is hydrogen;

 $\rm R^{5}$ and $\rm R^{6}$ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl,

cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^{9} , $S(O)R^{9}$, $SO_{2}R^{9}$, and $SO_{3}R^{9}$,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more

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substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, oR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₂R¹³, SO₂R¹³, SO₂R¹³, NR¹³OR¹⁴, NR¹³R¹⁴, C(O) NR¹³R¹⁴, C(O) NR¹³R¹⁴, C(O) NR¹³R¹⁴, C(O) NR¹³R¹⁴, D(O) NR¹³R¹⁴, NR¹³SO₁R¹³, NR¹³SO₁R¹⁴, P(O) R¹³R¹⁴, Pr¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻, wherein:

A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, CO₂R⁷, CN, OXO, CONR⁷R⁸, N⁴R⁷R⁸P⁸A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, p(O)R⁷R⁸, p⁴R⁷R⁸P⁹A⁻, and P(O)(OR⁷)OR⁸, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R⁷, P⁺R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkylheteroarylalkyl, polyether, aryl, arylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle,

alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary

alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl heteroaryl, heterocyclylalkyl, heteroarylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl,

acid, peptide, or polypeptide, and pR^9 , $p^+R^9R^{10}A$ -, $P(0)R^*$, phenylene, carbohydrate, aminc carbons replaced by O, NR, N+R9R10A-, S, SO, SO2, S+R9A; heterocycle, and polyalkyl optionally have one or more

 $P^{+}R^{9}R^{10}R^{11}A^{-}$, $S^{+}R^{9}R^{10}A^{-}$, and C(0)OM, $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, OXO_{7} , OXO_{7} , OXO_{7} guanidinyl, carboxyalkylheterocyclylthio, oR⁹, NR⁹R¹⁰, heterocyclylalkyl, quaternary heteroarylalkyl heterocycle, quaternary heteroaryl, quaternary one or more groups selected from the group consisting of halogen, $conr^9 r^{10}$, $so_2 om$, $so_2 ur^9 r^{10}$, $po(or^{16}) or^{17}$ heterocycle, heteroaryl, sulfoalkyl, quaternary hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, $m R^{13}, \ R^{14}, \ and \ R^{15}$ are optionally substituted with

the substituents constituting R^9 and M; or wherein \mathbb{R}^{16} and \mathbb{R}^{17} are independently selected from

quaternary salts; or selected from the group consisting of oxo, carboxy and that is optionally substituted with one or more radicals they are attached form a mono- or polycyclic heterocycle R" and R", together with the nitrogen atom to which

which they are attached, form a cyclic ring; and ${\mathbb R}^{14}$ and ${\mathbb R}^{15}$, together with the nitrogen atom to

alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, R³⁰ is selected from the group consisting of alkyl

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carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R' and R' are hydrogen; and

 $C(0)NR^{13}R^{14}$, $NR^{14}C(0)R^{13}$, C(0)OM, COR^{13} , OR^{16} , $S(0)_{n}NR^{16}$, NR11R14, SR11, S(0)R11, S(0)2R11, SO3R11, S'R11R14A', NR11OR14, quaternary heterocycle, quaternary heteroaryl, OR13 group consisting of H, alkyl, alkenyl, alkynyl peptide, polypeptide, and carbohydrate, NR11R18, NR18OR14, N'R9R11R13A', P'R9R11R12A', amino acid, NR11NR14R15, NO2, CO2R11, CN, OM, SO2OM, SO2NR13R14, NR14C(O)R11, cycloalkyl, heterocycle, heteroaryl, polyether, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, one or more R^* are independently selected from the

halogen, CONR°R10, SO,OM, SO,NR°R10, PO(OR14)OR17, P'R°R11R12A $N^*R^3R^{11}R^{12}A^{-}$, SR^9 , $S(0)R^9$, SO_2R , SO_3R^9 , OXO_7 , CO_2R^9 , CN, polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, S'R'R'A', or C(0)OM, and heteroaryl can be further substituted with OR', NR'R'0 wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

heteroaryl, and alkyl, acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein R10 is selected from the group consisting of

SO,NR°R10, PO(OR16)OR17, and C(O)OM, SO,R', oxo, CO,R', CN, halogen, CONR'R', SO,R', SO,OM, consisting of OR', NR'R'', N'R'R''R''A', SR', S(O)R', SO,R' one or more substituents selected from the group and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl,

polypeptide, carbohydrate, polyether, or polyalkyl, P(O)R13, P'R13R14A', phenylene, amino acid, peptide, replaced by O, NR11, N'R11R14A', S, SO, SO, S'R11A', PR11 wherein in R*, one or more carbons are optionally wherein in said polyalkyl, phenylene, amino acid

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peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR', N'R'R'A', S, SO, SO, S'R'A', PR', P'R'R'A', or P(O)R';

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹¹, NR¹¹R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³R¹⁴, NO₃, CO₃R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, P(O)R¹³R¹⁴, P(R¹³R¹⁴R¹⁴, P(O)R¹³R¹⁴R¹⁵, and N'R¹R¹³R¹⁴.

106. The process of claim 105 wherein the cyclic sulfate has the formula:

χŗ

and the thiophenol has the formula:

XVIIIA

z...

wherein R1, R3, R3 and q are as defined in claim

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105.

107. The process of claim 105 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.

108. The process of claim 107 wherein the hydrolyzing agent is a mineral acid.

109. The process of claim 107 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.

110. The process of claim 106 wherein the abstracting agent is a base having a pH of at least about 10.

111. The process of claim 106 wherein the abstracting agent is an alkali metal hydride.

112. The process of claim 106 wherein the abstracting agent is sodium hydride.

113 The process of claim 106 wherein R^1 and R^2 are independently selected from alkyl.

114. The process of claim 106 wherein R¹ and R¹ are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

115. The process of claim 106 wherein \mathbb{R}^1 and \mathbb{R}^2 are n-butyl.

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having the formula I: 116. A process for the preparation of a compound

$$\begin{bmatrix} O \\ h \end{bmatrix}_{\Pi} R^{7}$$

$$\begin{bmatrix} A \\ h \end{bmatrix}_{\Pi} R^{7}$$

$$A \\ A \\ A \end{bmatrix}$$

 $\widehat{\Xi}$

reacting a cyclic sulfate with a thiophenol to form

oxidizing said alcohol to form a sulfone-aldehyde;

of formula I;

cyclizing said sulfone-aldehyde to form the compound

wherein:

q is an integer from 1 to 4;

alkylthio, (polyalkyl)aryl, and cycloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, R^1 and R^2 are independently selected from the group

alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are and CONR'R10, , p'R'R''R''A', S(0)R', SO,R', SO,R', CO,R', CN, halogen, oxo, the group consisting of OR', NR'R'', N'R'R'A', SR', S'R'R''A'. substituted with one or more substituents selected from alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, wherein alkyl, alkenyl, alkynyl, haloalkyl,

have one or more carbons replaced by O, NR, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy

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cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or carboxyalkylaminoalkyl, heteroarylalkyl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino arylalkyl, carboxyalkyl, carboxyheteroaryl, from the group consisting of H, alkyl, alkenyl, alkynyl, R^1 and R^2 taken together with the carbon to which $N^*R^*R^{10}A^-$, S, SO, SO₃, S'R*A⁻, P'R*R¹⁰A⁻, or phenylene wherein R*, R10, and R* are independently selected

R' is hydroxy;

they are attached form C₃-C₁₀ cycloalkyl;

R4 is hydrogen;

cycloalkyl, heterocycle, quaternary heterocycle, OR 30, consisting of H, alkyl, alkenyl, alkynyl, aryl, $\ensuremath{\text{R}}^5$ and $\ensuremath{\text{R}}^6$ are independently selected from the group

sR⁹, s(0)R⁹, so₂R⁹, and so₃R⁹,

 ${\rm SO_{3R}^{13}}$, ${\rm NR}^{13}{\rm OR}^{14}$, ${\rm NR}^{13}{\rm NR}^{14}{\rm R}^{15}$, ${\rm NO_{2}}$, ${\rm CO_{2}R}^{13}$, ${\rm CN}$, ${\rm OM}$, arylalkyl, quaternary heterocycle, quaternary heteroaryl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, consisting of alkyl, alkenyl, alkynyl, polyalkyl, substituent groups independently selected from the group heteroaryl can be substituted with one or more heterocycle, quaternary heterocycle, and quaternary halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

p⁺R¹³R¹⁴R¹⁵A⁻, p(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻, NR13502R14, NR1350NR14R15, NR13502NR14R15, P(0)R13R14 NR11C(0)NR14R15, NR11CO,R14, OC(0)R11, OC(0)NR11R14, NR11SOR14, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13} , $NR^{12}C(O)R^{14}$,

A is a pharmaceutically acceptable anion and M is a

pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR⁷, S(O)R⁷, SO₂R⁷, CO₂R⁷, CN, oxo, CONR⁷R⁸, N⁴R⁸R⁹A-, alkyl, alkenyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heterocycle, p(O)R⁷R⁸, p⁴R⁷R⁸R⁹A⁻, and P(O) (OR⁷)OR⁸, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N⁺R⁷8⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(O)R⁷, P⁺R⁷R⁸A-, or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylaterylalkyl, polyalkyl, heterocycle, alkylaterocyclylalkyl, cycloalkyl, heterocycle, heterocyclylalkyl, cycloalkyl, heterocycle, heterocyclylalkyl, heterocycle, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, alkylamminocarbonylalkyl, alkylammoniumalkyl, and carboxyalkylamminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by 0, NR', N † R 10 A-, s, SO, SO2, S † R 9 A, pR 9 , p † R 9 R 10 A-, P(0)R 9 , phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R13, R14, and R15 are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary

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heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, carboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺R⁹R¹⁰R⁻, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and $\text{M}_{\text{\tiny J}}$ or

R¹³ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 $R^{\mbox{\scriptsize 1}}^{\mbox{\scriptsize 4}}$ and $R^{\mbox{\scriptsize 1}}^{\mbox{\scriptsize 5}}$, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyheteroaryl, carboxyheterocycle, carboxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R' and R' are hydrogen; and

one or more R" are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, whink!", SR", S(0)R", S(0)R", SO,R", S'R", R", NR"OR", NR", NO,, CO,R", CN, OM, SO,OM, SO,NR"R", NR"C(0)R", C(0)NR", NR"C(0)R", C(0)OM, COR", OR", S(0)R", NR"R", NR"C(0)R", NR"R", NR"R", NR"C(0)R", C(0)OM, COR", S(0)R", S(0)R", NR"R", NR"R

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

S'R'R10A', or C(0)0M, and halogen, CONR'R'', SO,OM, SO,NR'R'', PO(OR'')OR'', P'R'R''R''A' N'R'R11R12A', SR', S(0)R', SO2R, SO3R', OXO, CO2R', CN, heteroaryl can be further substituted with OR, NR'R10, polyether, quaternary heterocycle, and quaternary polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl,

heteroaryl, and alkyl, acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, wherein R16 is selected from the group consisting of

SO,NR R 10, PO (OR 16) OR 17, and C (O) OM, SO,R, oxo, CO,R, CN, halogen, CONR,R, SO,R, SO,OM, consisting of OR', NR'R'', N'R'R''R''A', SR', S(O)R', SO,R', one or more substituents selected from the group and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, wherein acyl, arylalkoxycarbonyl, arylalkyl

polypeptide, carbohydrate, polyether, or polyalkyl, P(O)R11, P'R11R14A', phenylene, amino acid, peptide, replaced by O, NR11, N'R112R'1A', S, SO, SO, S'R11A', PR11, wherein in R*, one or more carbons are optionally

SO2, S'R'A', PR', P'R'R'OA', or P(O)R'; carbons are optionally replaced by O, NR*, N'R*R¹ºA', S, SO, peptide, polypeptide, and carbohydrate, one or more wherein in said polyalkyl, phenylene, amino acid,

P(O)R13R14, P'R13R14R15A', P(OR13)OR14, S'R13R14A', and N'R18R14R14A' CO2R13, CN, OM, SO2OM, SO2NR13R14, C(O)NR13R14, C(O)OM, COR13, NR13R11, SR13, S(0)R13, SO2R13, SO3R13, NR13OR11, NR13NR14R15, NO2. cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR11, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, groups selected from the group consisting of alkyl, heteroaryl are optionally substituted with one or more wherein quaternary heterocycle and quaternary

sulfate has the formula: 117. The process of claim 116 wherein the cyclic

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and the thiophenol has the formula:

wherein R', R', R', R' and q are as defined in claim

independently selected from alkyl. 118. The process of claim 117 wherein R1 and R2 are

ethyl, n-butyl, iso-butyl and pentyl. R^2 are independently selected from the group consisting of 119. The process of claim 117 wherein wherein R1 and

n-butyl. 120. The process of claim 117 wherein R' and R' are

is oxidized with an oxidizing agent to form an aldehyde 121. The process of claim 117 wherein the alcohol

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122. The process of claim 121 wherein the aldehyde is oxidized with an oxidizing agent to form a sulfonealdehyde.

- 123. The process of claim 117 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is a base having a pH between about 8 to about 9.
- 124. The process of claim 117 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is an alkali alkoxide base.
- 125. The process of claim 117 wherein the sulfone-aldehyde is cyclized with potassium tert-butoxide.
- 126. The process of claim 117 wherein the alcohol is oxidized with pyridinium chlorochromate to form an aldehyde; the aldehyde is oxidized with metachloroperbenzoic acid to form a sulfone-aldehyde; and the sulfone-aldehyde is cyclized with potassium textbutoxide.
- 127. A process for the preparation of a compound having the formula L1:

comprising:

treating a halobenzene with an abstracting agent; coupling the halobenzene and a cyclic sulfate to form an intermediate comprising a sulfate group; and

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removing the sulfate group of the intermediate to form the compound of formula LI; wherein

q is an integer from 1 to 4;

R¹ and R¹ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR', NR'R'', NR'R''R', SR', S'R'R'', PR'R'R'', S(O)R', SO,R', SO,R', CO,R', CN, halogen, oxo, and CONR'R'',

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl) aryl, and cycloalkyl optionally have one or more carbons replaced by 0, NR',

N'R'R''9', S, SO, SO, S'R'A', P'R'R''9', or phenylene, wherein R', R'', and R' are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylaminoalkyl, heteroarylalkyl, and alkylammoniumalkyl, or

R' and R' taken together with the carbon to which they are attached form G,-C, cycloalkyl;

R' is hydroxy;

R* is hydrogen;

 R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, Ω^{30} , Ω^{8} , Ω^{2} , Ω^{2} , and Ω^{3R} ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,

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heterocycle, quaternary heterocycle, and quaternary heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, oR¹³, NR¹³R¹⁴, SR¹³, S(0)R¹³, SO₂R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(0)NR¹³R¹⁴, C(0)OM, COR¹³, NR¹³COR¹⁴, NR¹³COR¹⁴, NR¹³COR¹⁴, NR¹³COR¹⁴, NR¹³SOR¹⁴, NR¹³SONR¹⁶, NR¹³SO₂NR¹⁶, NR¹³SONR¹⁶, NR¹³SO₂NR¹⁶, and N⁺R⁹R¹¹R¹²A⁻, wherein:

A is a pharmaceutically acceptable anion and M is pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, OXO, $CONR^7R^8$, $N^+R^7R^8R^9A$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by 0, NR⁷, N⁺R⁷R⁸A-, S, SO, SO₂, S⁺R⁷A-, PR⁷, P(0)R⁷, P⁺R⁷R⁸A- or phenylene, and R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen, alkyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl,

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alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl,

heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', N⁺R⁹R¹⁰A-, S, SO, SO₂, S⁺R⁹A', PR⁹, P⁺R⁹R¹⁰A-, P(O)R', phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R¹³, R¹⁴, and R¹⁵ are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guandinyl, carboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(0)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰, PO(OR¹⁶)OR¹⁷, p⁺R⁹R¹⁰R¹¹A-, s⁺R⁹R¹⁰A-, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M_i or

R13 and R14, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 κ^{14} and $\kappa^{15},$ together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle,

carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, heterocyclylalkyl, and alkylammoniumalkyl; and ammoniumalkyl, alkylammoniumalkyl, arylalkyl, R' and R' are hydrogen; and

NR¹¹NR¹⁴R¹⁵, NO,, CO₃R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C (O) R¹³, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, one or more R* are independently selected from the NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)₃R¹³, SO₃R¹³, S'R¹³R¹⁴A', NR¹³OR¹⁴, quaternary heterocycle, quaternary heteroaryl, OR¹³, C(0) NR11814, NR14C(0) R11, C(0) OM, COR11, OR16, S(0) NR16, NR13R18, NR18OR14, N'R8R11R13A', P'R8R11R13A', amino acid, cycloalkyl, heterocycle, heteroaryl, polyether, group consisting of H, alkyl, alkenyl, alkynyl, peptide, polypeptide, and carbohydrate,

halogen, $CONR^8R^{10}$, SO_2OM , $SO_3NR^9R^{10}$, $PO\left(OR^{16}\right)OR^{17}$, $P^*R^9R^{11}R^{13}A^-$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, heteroaryl can be further substituted with OR', NR'R'", polyether, quaternary heterocycle, and quaternary N'R'R11R13A', SR', S(0)R', SO1R', SO1R', OXO, CO1R', CN, S'R'R10A', or C(O)OM, and

wherein R' is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

and quaternary heteroaryl optionally are substituted with heterocycle, heteroaryl, alkyl, quaternary heterocycle, consisting of OR', NR'R'', N'R'R''R'A', SR', S(0)R', SO3R', SO,R', oxo, CO,R', CN, halogen, CONR'R'', SO,R', SO,OM, wherein acyl, arylalkoxycarbonyl, arylalkyl, one or more substituents selected from the group SO₂NR³R¹⁰, PO(OR¹⁶)OR¹⁷, and C(O)OM,

wherein in R", one or more carbons are optionally replaced by O, NR11, N'R11R1'A, S, SO, SO, S'R13A', PR11, P(O)R", P'R"R'A, phenylene, amino acid, peptide,

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polypeptide, carbohydrate, polyether, or polyalkyl,

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carbons are optionally replaced by O, NR', N'R'R'A', S, SO, wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more SO2, S'R'A", PR', P'R'R'A", or P(O)R';

P(0)R13R14, P'R13R14R13A', P(0R13)OR14, S'R13R14A', and N'R'R13R13A', NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₃R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₃, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, CO_2R^{13} , CN, OM, SO_2OM , $SO_3NR^{13}R^{14}$, C(O) $NR^{13}R^{14}$, C(O) OM, COR^{13} , heteroaryl are optionally substituted with one or more cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹¹ groups selected from the group consisting of alkyl, wherein quaternary heterocycle and quaternary

R is an electron-withdrawing group located at the para or ortho position. 128. The process of claim 127 wherein the cyclic sulfate has the formula:

and the halobenzene has the formula:

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wherein R^h is halogen, and R^1 , R^2 , R^3 , R^3 , R^4 , R^4 and q are as defined in claim 127.

- 129. The process of claim 128 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.
- 130. The process of claim 129 wherein the hydrolyzing agent is a mineral acid.
- 131. The process of claim 129 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.
- 132. The process of claim 128 wherein the abstracting agent is a dialkali metal sulfide.
- 133. The process of claim 128 wherein the abstracting agent is dilithium sulfide.
- 134. The process of claim 128 wherein wherein R^1 and R^2 are independently selected from alkyl.
- 135. The process of claim 128 wherein R¹ and R² are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.
- 136. The process of claim 128 wherein R^1 and R^2 are n-butyl.
- 137. The process of claim 128 wherein Rh is chloro
- 138. The process of claim 128 wherein R° is p-nitro
- 139. A process for the preparation of a compound

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having the formula I:

$$R^{y_{0}} = \begin{bmatrix} & & & & & \\ & & & \\ & & & & \\ & & &$$

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comprising:

reacting a cyclic sulfate with a halobenzene to form
an alcohol;

oxidizing said alcohol to form a sulfone-aldehyde;

cyclizing said sulfone-aldehyde to form the compound of formula I;

wherein

q is an integer from 1 to 4;

n is 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl) aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR*, NR*R¹O, N'R*R¹O,' SR*, S'R*R¹O, P'R*R¹O, S(O)R*, SO,R*, SO,R*, CO,R*, CN, halogen, oxo, and CONR*R¹O,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR,

N'R'R' ^{0}A ', S, SO, SO, S'R ^{9}A ', P'R'R ^{10}A ', or phenylene, wherein R 9 , R 10 , and R 8 are independently selected

from the group consisting of H, alkyl, alkenyl, alkynyl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyalkylaminoalkyl, heteroarylalkyl,

R' and R' taken together with the carbon to which they are attached form C,-C, cycloalkyl;

R' is hydroxy;

R' is hydrogen;

R⁵ and R⁶ are independently selected from the group cycloalkyl, heterocycle, quaternary heterocycle, $\mathtt{OR}^{\mathtt{JO}}$ consisting of H, alkyl, alkenyl, alkynyl, aryl, SR⁹, S(0) R⁹, SO₂R⁹, and SO₃R⁹,

arylalkyl, quaternary heterocycle, quaternary heteroaryl, ${
m SO_2OM}$, ${
m SO_2NR^{13}R^{14}}$, ${
m C(0)\,NR^{13}R^{14}}$, ${
m C(0)\,OM}$, ${
m COR^{13}}$, ${
m NR^{13}C(0)\,R^{14}}$, $p^{+}R^{13}R^{14}R^{15}A^{-}$, $p(0R^{13})0R^{14}$, $s^{+}R^{13}R^{14}A^{-}$, and $N^{+}R^{9}R^{11}R^{12}A^{-}$, substituent groups independently selected from the group wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, NR11C(0) NR14R15, NR12CO3R14, OC(0) R13, OC(0) NR13R14, NR13SOR14, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, halogen, \cos , \cos^{13} , $\sin^{13}\!\mathrm{R}^{14}$, \sin^{13} , $\mathrm{S}(\mathrm{O})\,\mathrm{R}^{13}$, $\mathrm{SO}_2\mathrm{R}^{13}$, heterocycle, quaternary heterocycle, and quaternary 503R¹³, NR¹³0R¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, consisting of alkyl, alkenyl, alkynyl, polyalkyl, heteroaryl can be substituted with one or more 4 180 1 180 1 180 1 180 1 180 1 180 1 180 1 180 1 180 1 180 1 180 1 180 1

A is a pharmaceutically acceptable anion and M is a said alkyl, alkenyl, alkynyl, polyalkyl, polyether, pharmaceutically acceptable cation,

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S(0)R7, SO2R7, SO3R7, CO2R7, CN, OXO, CONR7R8, N+R7R8R9-A-, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 aryl, haloalkyl, cycloalkyl, and heterocycle can be

arylalkyl, quaternary heterocycle, quaternary heteroaryl

NR7, N+R7R8A-, S, SO, SO2, S+R7A-, PR7, P(O)R7, P+R7R8Apolyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, wherein said alkyl, alkenyl, alkynyl, polyalkyl, or phenylene, and \mathbb{R}^{13} , \mathbb{R}^{14} , and \mathbb{R}^{15} are independently P(0)R⁷R⁸, P⁺R⁷R⁸R⁹A⁻, and P(0) (OR⁷)OR⁸, and

quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, selected from the group consisting of hydrogen, alkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, heterocyclylalkyl, heteroarylalkyl, heteroaryl, quaternary heterocycle, quaternary alkylarylalkyl, alkylheteroarylalkyl,

carbons replaced by O, NR', N'R'9R10A-, S, SO, SO2, S'R'9A', heterocycle, and polyalkyl optionally have one or more PR^{9} , $P^{+}R^{9}R^{10}A_{-}$, $P(0)R^{9}$, phenylene, carbohydrate, amino wherein alkyl, alkenyl, alkymyl, arylalkyl, acid, peptide, or polypeptide, and

one or more groups selected from the group consisting of R¹³, R¹⁴, and R¹⁵ are optionally substituted with guanidinyl, carboxyalkylheterocyclylthio, OR⁹, NR⁹R¹⁰, hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl,

 $N^{+}R^{9}R^{11}R^{12}A^{-}$, SR^{9} , $S(0)R^{9}$, $SO_{2}R^{9}$, $SO_{3}R^{9}$, OXO, $CO_{2}R^{9}$, CN, halogen, $CONR^{9}R^{10}$, $SO_{2}OM$, $SO_{2}NR^{9}R^{10}$, $PO(OR^{16})OR^{17}$, $P^{+}R^{9}R^{10}R^{11}A^{-}$, $S^{+}R^{9}R^{10}A^{-}$, and C(O)OM,

wherein ${\bf R}^{16}$ and ${\bf R}^{17}$ are independently selected from the substituents constituting ${\bf R}^9$ and M; or

R¹³ and R¹⁴, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

 ${\mathbb R}^{14}$ and ${\mathbb R}^{15}$, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R¹⁰ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyheteroaryl, carboxyheterocycle, carboxyalkyl, carboxyheteroaryl, carboxyheteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R' and R' are hydrogen; and

one or more R* are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹¹, NR¹¹R¹¹, S(O)R¹¹, S(O)₂R¹¹, SO₃R¹¹, S'R¹¹R¹⁴, NR¹¹OR¹⁴, NR¹¹C(O)R¹³, CN, OM, SO₃OM, SO₃NR¹¹R¹⁴, NR¹⁴C(O)R¹³, C(O)OM, COR¹³, OR¹⁴, S(O)₂NR¹⁴, NR¹⁴C(O)R¹³, NR¹⁴R¹⁴, NR¹⁴C(O)R¹³, CO₃O₃OM, SO₃OM, SO₃OM, SO₃OM, SO₃OM, NR¹⁴R¹⁴, NR¹⁴C(O)R¹³, OR¹⁴, NR¹⁴C(O)R¹³, CO₃O₃OM, COR¹³, OR¹⁴, S(O)₂MR¹⁴, NR¹⁴C(O)R¹³, CO₃O₃OM, COR¹³, OR¹⁴, S(O)₂MR¹⁴, NR¹⁴C(O)R¹³, OR¹⁴, P'R¹R¹³A, P'R¹R¹³A, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR*, NR*R10,

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N'R'R11R12A', SR', S(0)R', SO,R, SO,R', OXO, CO,R', CN, halogen, CONR'R10', SO,OM, SO,NR'R10', PO(OR10)OR1', P'R'R11R12A', S'R'R10A', OT C(0)OM, and

wherein \mathbf{R}^{11} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR*, NR*R¹0, N'R*R¹1R¹A', SR*, S(O)R*, SO,R*, SO,R*, OXO, CO,R*, CN, halogen, CONR*R¹0, SO,R*, SO,OM, SO,NR*R¹0, PO(OR¹4)OR¹7, and C(O)OM,

wherein in R*, one or more carbons are optionally replaced by O, NR¹³, N'R¹³R'*A', S, SO, SO, S'R¹³A', PR¹³, P(O)R¹³, P'R¹³R''A', phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR, N'R, R, S, SO, S'R, A', PR, P,R, R, Or P(O)R,

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹¹, NR¹¹R¹⁴, SR¹¹, S(O)R¹¹, SO₂R¹¹, SO₂R¹¹, NR¹¹OR¹⁴, NR¹¹NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹¹R¹⁴, C(O)NR¹¹R¹⁴, C(O)OM, COR¹³, P(O)R¹¹R¹⁴, P'R¹¹R¹⁴A⁻, and N'R²R¹¹R¹³A⁻, and

 $\ensuremath{\mathtt{R}}^\bullet$ is an electron-withdrawing group located at the para or ortho position.

140. The process of claim 139 wherein the cyclic sulfate has the formula;

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and the halobenzene has the formula:

wherein $R^1,\ R^2,\ R^3$ and R^n are as defined in claim 139, and R^h is halogen.

- 141. The process of claim 140 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.
- 142. The process of claim 141 wherein the hydrolyzing agent is a mineral acid.
- 143. The process of claim 140 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.
- 144. The process of claim 140 wherein the abstracting agent is a dialkali metal sulfide.
- 145. The process of claim 140 wherein the abstracting agent is dilithium sulfide.

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- 146. The process of claim 140 wherein wherein R^{1} and R^{2} are independently selected from alkyl.
- 147. The process of claim 140 wherein R' and R' are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.
- 148. The process of claim 140 wherein \mathbb{R}^1 and \mathbb{R}^2 are n-butyl.
- 149. The process of claim 140 wherein Rb is chloro.
- 150. The process of claim 140 wherein R' is p-nitro.
- 151. The process of claim 140 wherein the alcohol is oxidized with an oxidizing agent to form a sulfone.
- 152. The process of claim 140 wherein the sulfone is oxidized with an oxidizing agent to form a sulfonealdehyde.
- 153. The process of claim 140 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is a base having a pH between about 8 to about 9.
- 154. The process of claim 140 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is an alkali alkoxide base.
- 155. The process of claim 140 wherein the sulfone-aldehyde is cyclized with potassium tert-butoxide.
- 156. The process of claim 140 wherein the alcohol is oxidized with metachloroperbenzoic acid to form a

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sulfone; the aldehyde is oxidized with pyridinium chlorochromate to form a sulfone-aldehyde; and the sulfone-aldehyde is cyclized with potassium tertbutoxide.

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INTERNATIONAL SEARCH REPORT

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Pax: (~31~70) 340~30 18 Fax: (~31~70) 340~30 18	and mating address of the ISA European Petent Office, P.B. 5618 Patentisen 2 NL - 2209 PM Filevill, Tel. (+31-70) 340-2040, Tr. 31 851 apo nl	October 1999	of the actual completion of the international search	**Cocument deliving the general state of the art which is not consistent to be of pullicular relevance **Commission to be of pullicular relevance **Cocument deliver to be of pullicular relevance **Cocument which may throw decide on potenty claim(s) or which is died to establish the publication date of another estation or other special reason (as specials) **Cocument relevance of on oral decidence, use, exhibition or other means **Pot document published price to the international flang date but learn than the procesy date claimed.	Further documents are falled in the continuation of box C.	WO 99 32478 A (6.D. SEARLE) 1 July 1999 (1999-07-01) the whole document	WO 98 40375 A (G.D. SEARLE) 17 September 1998 (1998-09-17) page 66 -page 127; claims; example 1400	WO 96 08484 A (MONSANTO) 21 March 1996 (1996-03-21) the whole document	WO 97 33882 A (G.D. SEARLE) 18 September 1997 (1997-09-18) page 75 -page 183; claims	Caston of document, with indication, where appropriate, of the relevant passages	C. DOCUMENTS CONSIDERED TO BE RELEVANT	Documentation exercised other than minimum documentation to the extent that each documents are included in the felicle searched	Information described (classification system followed by classification symbols) IPC 7 C07D C07K C07F A61K	1FC / C0/1033//08 C070487/08 C070409/12 C1 C0719/6553 C07C323/18 A61K31/38 C070709/6553 C07C323/18 A61K31/38 C070709/01 in the material plant Classification (PC) or to both national dasself-action and IPC and page 16000000000000000000000000000000000000	- 1
rrancois, J		08/11/1999	Date of mailing of the international search report	The last occurrent published star the treamational sting date property of the control with the application four called to understand the property of theory underlying the workship of the property of the control to control the property of the control to control to control to control to control to control and control to control to control and property of the control to control and property of the control to control and property of the control to the control and provided the control of the control o	X Patent family members are listed in annex.	·	Te 1400			elevant passages	see art, wee product, sarch turns up	d such documents are included in the fision	ation symbole)	070409/10	1
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INTERNATIONAL SEARCH REPORT

mational application No.

Box I Observations where certain claims were found unsearchable (Continuation of Isam 1 of first sheet) PCT/US 99/12828

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following seasons:	2)(a) for the following reasons:
2. Claims Now.: 99 to 101 Remark: Although claims 99 to 101 Remark: Although claims 99 to 101 are directed to a diagnostic method practised of the human/ani body, the search has been carried out and based on the alleged effects of the compound/composition. Claims Nos.: Claims Nos.: boccuse Device the bis mismatorial Appleation that so not comply with the prescribed requirements to such an artent that no meaningful international Appleation that so not comply with the prescribed requirements to such	actised of the human/animal and based on the alleged with the prescribed requirements to such y.
3.	d semences of Ruis 6.4(a).
The International Searching Authority found multiple inventions in this international application, as follows:	Æ
As all required additional search less were timely paid by the applicant, this International Search Report covers all searchable claims. As all searchable claims could be searched without effort justifying an additional ise, this Authority did not trylis payment of any additional ise.	h Report covers all frequent covers all frequent fry dd not invite payment
 As only some of the required and from I search less were timely paid by the applicant, this International Search Raport covers only those claims for which free were paid, specifically claims Nos.: 	halforial Search Raport
 No required additional search hees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention frest mentioned in the chaints; it is covered by chains Nos.: 	ional Searth Report is
Remark on Protest The additional search less were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.	ed by the applicant's protest. Altonel search fees.
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